


REVIEW

Open Access



Recent advances on the molecular mechanisms of exercise-induced improvements of cognitive dysfunction

Yi Lu[†], Fa-Qian Bu[†], Fang Wang[†], Li Liu, Shuai Zhang, Guan Wang^{*}  and Xiu-Ying Hu^{*}

Abstract

Physical exercise is of great significance for maintaining human health. Exercise can provide varying degrees of benefits to cognitive function at all stages of life cycle. Currently, with the aging of the world's population and increase of life expectancy, cognitive dysfunction has gradually become a disease of high incidence, which is accompanied by neurodegenerative diseases in elderly individuals. Patients often exhibit memory loss, aphasia and weakening of orientation once diagnosed, and are unable to have a normal life. Cognitive dysfunction largely affects the physical and mental health, reduces the quality of life, and causes a great economic burden to the society. At present, most of the interventions are aimed to maintain the current cognitive level and delay deterioration of cognition. In contrast, exercise as a nonpharmacological therapy has great advantages in its nontoxicity, low cost and universal application. The molecular mechanisms underlying the effect of exercise on cognition are complex, and studies have been extensively centered on neural plasticity, the direct target of exercise in the brain. In addition, mitochondrial stability and energy metabolism are essential for brain status. Meanwhile, the organ-brain axis responds to exercise and induces release of cytokines related to cognition. In this review, we summarize the latest evidence on the molecular mechanisms underlying the effects of exercise on cognition, and point out directions for future research.

Keywords Exercise, Cognitive function, Molecular mechanism, Neurodegenerative disease, Nonpharmacological therapy

Background

Cognitive decline occurs during the aging process. It is often observed in two populations, the elderly people with mild cognitive impairment (MCI) and cognitive

dysfunction, and patients with neurodegenerative diseases [1, 2]. The prevalence of MCI increases with age (6.7% for ages 60–64, 8.4% for 65–69, 10.1% for 70–74, 14.8% for 75–79, and 25.2% for 80–84) [1]. Cognitive dysfunction is frequently seen in neurodegenerative diseases, and the high incidence of neurodegenerative diseases increases the prevalence of cognitive dysfunction. There were 35.6 million people diagnosed with dementia in 2010 worldwide [3], and this figure is expected to double every 20 years [4], which will reach 65.7 million in 2030 and 150 million in 2050 [5]. At present, the cost of care for current 35 million patients with dementia is over \$600 billion per year, accounting for approximately 1% of the global gross domestic product [6]. Apart from dementia, cognitive impairment is also identified in

[†]Yi Lu, Fa-Qian Bu and Fang Wang contributed equally to this review

*Correspondence:

Guan Wang
guan8079@163.com
Xiu-Ying Hu
huxiuying@scu.edu.cn

West China School of Nursing, Sichuan University/Innovation Center of Nursing Research, Nursing Key Laboratory of Sichuan Province, State Key Laboratory of Biotherapy and Cancer Center, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu 610041, China



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

34%–65% of people with multiple sclerosis (MS), and 40% with Parkinson's disease (PD) [7, 8].

Neurobiological features of cognitive impairment are specific among different diseases. Brain plasticity deficits are often observed in age-related cognitive impairment. The hippocampus plays a key role in brain plasticity and has a classical trisynaptic circuit. The entorhinal cortex provides the major cortical input to the hippocampus, and the cross-projections between dentate gyrus (DG), cornu ammonis 1 (CA1) and cornu ammonis 3 (CA3) regions are critical for supporting a distributed memory [9]. Therefore, decreases of dendritic branching and synapses in the entorhinal cortex, DG and CA1-CA3 are characteristics of cognitive decline in aged population [10]. It is believed that extracellular aggregation of amyloid beta ($A\beta$) and intracellular aggregation of tau or formation of neurofibrillary tangles (NFTs) play a critical role in Alzheimer's type cognitive impairment [11]. Patients with Parkinson's type cognitive impairment show neuropathology of PD with early loss of dopaminergic neurons in the substantia nigra, and abnormal deposition of α -synuclein in Lewy bodies initially in cholinergic and monoaminergic neurons in the brainstem and the olfactory system, causing significant synaptic pathology [12]. There is similar neurobiology in other α -synucleinopathies, such as dementia with Lewy bodies (DLB) and multiple system atrophy [13]. For MCI, studies have shown hypoperfusion and hypometabolism in temporoparietal cortices, atrophy of the medial temporal lobe, elevation or phosphorylation of tau, decrease of $A\beta_{42}$ in the cerebrospinal fluid, and deposition of brain $A\beta_{42}$ [14]. Despite the differences in neurobiology, the age-related and disease-related cognitive dysfunction are consistent in pathophysiological features, including neuroinflammation, oxidative stress, mitochondrial dysfunction and metabolic alterations [15, 16].

Exercise therapy has been proven effective in promoting cognitive function [17], which can improve mental state such as depression and insomnia stress [18] and delay the progression of neurodegenerative diseases [19]. Different doses and types of exercise may have variable effects. Studies have reported the optimal dose and type of exercise to improve cognition in older adults and provided information that can be directly used to recommend the dose and type of exercise for optimal cognitive health among older adults [20]. A recent systematic review showed that there is no minimal threshold for beneficial effects of exercise on cognition, suggesting that any exercise dose is better than none. Notably, recent evidence also highlights superior effects of resistance exercises over other modalities [20]. Although most research was focused exclusively on aerobic exercise, resistance exercise

may also enhance cognition and brain outcomes in older adults [21]. Furthermore, a recent meta-analysis revealed that aerobic exercise combined with resistance training is the most effective to improve cognition among patients with MCI, whereas resistance exercise is the most effective for those with dementia [22]. The mechanisms of the effects of aerobic and resistance training on cognition may be different. For example, Vilela et al. observed increases of BDNF (brain-derived neurotrophic factor), cAMP-response element binding protein (CREB) and p75 neurotrophin receptor after training for both aerobic and resistance exercise in aging Wistar mice. In addition, glutamatergic proteins such as postsynaptic dense substance 95 (PSD-95) and NMDA receptor are increased only in aerobic rats, while resistance training increases levels of protein kinase C (PKC) as well as proinflammatory factors tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) in the hippocampus [23]. Meanwhile, exercise improves cognitive function in older adults in an intensity-dependent manner. Moderate-intensity exercise has been suggested as an optimal intensity for promotion of mental health by decreasing the level of TNF- α [24]. In contrast, strenuous exercise has been shown to enhance inflammation and trigger free radical-mediated damage [25]. Sanguesa et al. observed downregulation of oxidative phosphorylation of complex IV and AMP kinase (AMPK) activation in the cortex of rats after 16 weeks of intense exercise, denoting mitochondrial dysfunction [26].

The molecular mechanisms underlying the effects of exercise on cognitive function have been increasingly investigated. BDNF plays an important role in maintaining cognitive function and protecting nerve plasticity, and it is also an important molecular mediator of the neuroprotective effects of physical exercise [27]. In the pathological process of cognitive disorders, neuronal mitochondrial dysfunction often occurs [28], leading to excessive oxidative stress and energy deficiency in brain tissue. Exercise has been demonstrated to play an important role in improving the stability of neuronal mitochondria [29, 30]. Moreover, exercise can induce skeletal muscle production of myokines into the blood [31], some of which promote expression of BDNF in hippocampus and inhibit production of inflammatory factors [32]. In addition to the direct effects in the brain, such as neuroinflammation and oxidative stress, exercise can also stimulate energy metabolism in the brain [33] and the intestinal-brain axis [34]. In the following, we will summarize the significant and latest molecular mechanisms of the positive effect of exercise on cognitive function from the above-mentioned aspects.

Exercise enhances brain plasticity

Brain plasticity is the ability of the brain to reorganize its structure and function in response to learning, training and environment stimuli [35]. Brain plasticity includes changes in cortical thickness, gray matter volume, and white matter fiber connectivity strength and orientation at the macroscopic level; neuronal and synaptic morphological changes at the cellular level; changes in intracellular signals and gene transcription within the nucleus after stimulation at the molecular level. The mechanisms involved in plasticity in the nervous system are thought to support cognition [10]. The decline of brain structure and function in the elderly is the main cause of the decline of their cognitive function [36].

Neurotrophic factors and synaptic plasticity are critical mechanisms of brain plasticity. Neurotrophic factors are growth factors that can nourish neurons and promote neuron survival and regeneration [37]. Recent meta-analysis showed that blood levels of BDNF are decreased in PD and MS patients [38, 39]. Another primary functional alteration that could directly affect plasticity is reduced synaptic number, which could make it more difficult to attain sufficient number of cooperatively active synapses, which is necessary for network modification. It is appreciated that MCI in early Alzheimer's disease (AD) may be due to the synaptic dysfunction caused by accumulation of non-fibrillary, oligomeric A β , occurring prior to the evident widespread synaptic loss and neurodegeneration [40].

The maintenance of brain plasticity also depends on the nerve tissue. With progress of age-related neurodegenerative diseases, the number and function of brain nerve tissue begin to decrease, such as reduced phagocytic capacity of microglia, hyperplasia of astrocytes and microvascular changes in the DG of the hippocampus [41]. Recent evidence highlights that neurogenesis in the adult hippocampal body lasts until the tenth decade of human life [42]. Boldrini assessed the anterior, mid, and posterior parts of autopsy hippocampi from 28 healthy individuals (14 to 79 years of age), and characterized and quantified angiogenesis, volume, and cells in the DG neurogenic niche across ages, using unbiased stereological methods. Although the neuroplasticity declines in older individuals, they found that quiescent radial-glia-like type I neural progenitor cells (QNPs) decline, but the number of intermediate neural progenitors (INPs) remains stable, immature granule neurons (GNs) are preserved, and the numbers of mature GNs and glia as well as the DG volume remain unchanged during aging [43]. The QNPs and INPs mentioned above will continue to generate new neurons, a process called adult hippocampus neurogenesis (AHN). Se Hoon et al. found that exercise improves cognition in 5 \times FAD AD mice by inducing

AHN and increasing the level of BDNF [44]. These findings indicate that hippocampal neurogenesis exists in different stages of life, including in healthy older individuals.

During human aging, the decline of brain function is inevitable, but neural tissue has the capacity for plasticity and regeneration, which can resist the physiological and pathological decline in neurodegenerative diseases. Exercise is beneficial to brain function by enhancing hippocampal function [45, 46], increasing neurotrophic factors [47] and improving synaptic plasticity [48].

Exercise improves brain structure and function

The effect of exercise on the brain structure of the elderly is mainly reflected in the increase of the hippocampal volume. The hippocampus exhibits structural and functional changes in cognitive dysfunction. A meta-analysis including nine studies and 595 AD patients reported that the mean annualized hippocampal atrophy rates were 4.66% (95% CI 3.92, 5.40) for AD subjects and 1.41% (0.52, 2.30) for controls [49]. Recent studies have validated that aerobic and resistance exercise has a positive effect on the improvement of hippocampal volume. In a recent study by Schaeffer et al., 17 PD patients and 18 matched healthy controls were recruited to undertake a 6-week exergaming training program, which combined moderate-intensity aerobic fitness training with elements of coordination and speed. After training, the volumes of CA1, CA4 and DG were significantly increased in the left hippocampus in patients with PD. In particular, the DG region showed the most pronounced effect [50], which is consistent with the results from Frodl et al. [51]. Yun et al. also observed an increase of hippocampal volume after resistance training for 50–80 min a day, three times per week for a total of 24 weeks in elderly women [52]. Moreover, Cariati et al. observed well-organized neurons and glial cells, as well as nerve processes rich in neurotubules and neurofilaments in hippocampal slices of mice after 12 weeks of progressive continuous aerobic exercise [53]. In addition, aerobic exercise can lead to increased functional connectivity of the anterior putamen with the sensorimotor cortex, increased functional connectivity in the right frontoparietal network, and reduced global brain atrophy [54, 55]. A 9-year follow-up of nondemented older adults over 65 years found that walking 72 blocks per week (1600 m/day) leads to volume changes in the prefrontal cortex, parietal cortex, cerebellum, and hippocampus [56].

It is proven that physical exercise can also lead to the improvement of brain function. Alfini et al. found that 12-week treadmill training intervention improved performance in the auditory word learning test, the lexical association test scores, working memory and verbal fluency of MCI patients [57]. Tsai et al. showed that

vigorous aerobic exercise for 30 min at moderate intensity, corresponding to 65%–75% of the individual target heart rate reserve (HRR), improved cognitive functions including attention, recognition, decision-making, and memory of elderly adults [58]. A 6-week combined dance and relaxation intervention also enhances motor control and cognition, such as physical balance and attention, in older adults [59]. In older women complaining of memory decline, resistance training twice a week for 6 months improves selective attention, conflict resolution, associative memory and regional patterns of functional brain plasticity [60]. Kujawski et al. recruited healthy older participants in programs of sitting callisthenic balance and resistance training. After the 3-month resistance training program, the participants showed improved decision making, visual attention and global cognitive function [61].

BDNF: the key modulator between exercise and cognitive function

Neurotrophic factors in the brain may be the core modulator between exercise and cognitive function. BDNF is one of the most widely studied neurotrophic factors in the brain in mammalian health and diseases [62]. It is expressed in the hippocampus and released by glutamatergic neurons and glial cells (such as glial cells isolated from the cortical layer and hippocampus) [63], and is generally thought to be relevant to cognitive function. BDNF can promote axonal sprouting and new branching growth of motor units of the brain [64], enhance the growth of new branches of adjacent surviving neurons and promote generation of key structures around neuromuscular contacts to restore muscle-neuron communication [65, 66]. BDNF may play a critical role in the hippocampal synaptic long-term potentiation (LTP). The LTP is a long-term enhancement of synaptic efficacy thought to underlie learning and memory. BDNF also contributes to neurogenesis and neuronal survival [67]. Converging evidence suggests that deficits in BDNF signaling contribute to the pathogenesis of several major diseases with cognitive disorders, such as AD, Huntington disease (HD), and depression [68].

BDNF is produced in the brain, muscle and hematological system in humans. Current human studies mainly observe the increased level of peripheral BDNF after exercise [69, 70], which may be released from the muscle. In animal studies, increased BDNF content and mRNA have been detected in the hippocampus after exercise. In mice, exercise induces hippocampal BDNF through the proliferator-activated receptor gamma co-activator 1-alpha (PGC-1 α)/fibronectin type III domain protein 5 (FNDC5) pathway [71]. Meanwhile, exercise training protects against aging-induced cognitive dysfunction via

activation of the hippocampal PGC-1 α /FNDC5/BDNF pathway in rats [72].

BDNF is internalized into neurons mainly by binding to the primary receptor tropomyosin-related kinase B (TrkB), forming the BDNF/TrkB complex. TrkB is a single-channel type I membrane protein that can be incorporated into nuclear endosomes through ligand binding [73]. BDNF binds to TrkB and causes homodimerization and autophosphorylation of TrkB, leading to the recruitment of proteins containing PH and SH2 domains, such as fibroblast growth factor receptor substrate 2, Shc, SH2B and human SH2B adaptor protein 2. The recruited signaling intermediates initiate distinct intracellular signaling cascades and activate three major downstream signaling pathways, including phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and phospholipase C γ (PLC γ) intracellular cascades (Fig. 1). Through activation of these intracellular signaling pathways, exercise can resist the process of cognitive disorders in the central nervous system (CNS) [74]. PI3K regulates neuron growth and survival through activation of downstream protein kinase B (Akt) [75, 76]; the PLC γ -mediated pathway regulates synaptic plasticity through the downstream PKC signaling [77]; and the MAPK signaling pathway mainly regulates neuronal differentiation and neurite protrusion [78]. The Rat Sarcoma (RAS) signaling pathway, downstream of MAPK, regulates multiple cellular functions including proliferation. RAS binds to GTP via GDP-GTP exchange factors. RAS activity is also modulated by a complex array of extracellular signal-regulated protein kinase (ERK)-protein-kinase-dependent negative feedback loops [79] (Fig. 1). The negative feedback regulation coordinates the dynamic behavior of the Ras-Raf-MEK-ERK signal transduction pathway. Extensive animal experiments have demonstrated the effects of BDNF/TrkB signaling in improving cognitive function. Xu et al. reported that treadmill exercise could enhance learning and memory ability in healthy male Wistar rats through upregulation of serum BDNF and its receptor TrkB [80]. Timiga et al. found that short-term running exercise increased the levels of exon I and IV mRNA of BDNF in the hippocampus of C57BL/6J mice [81], and single form of exercise increased the level of exon IV mRNA of BDNF in an intensity-dependent manner [82]. Notably, Baranowski et al. demonstrated that exercise elevated BDNF levels in C57BL/6J mice, further reducing the activity of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), resulting in reduced A β production [83]. Therefore, it seems to be the increase of BDNF in the prefrontal cortex and hippocampus and the decrease of BACE1 after exercise that reverse the pathological amyloid deposition to some extent in the AD mice. These results suggest that exercise can act on

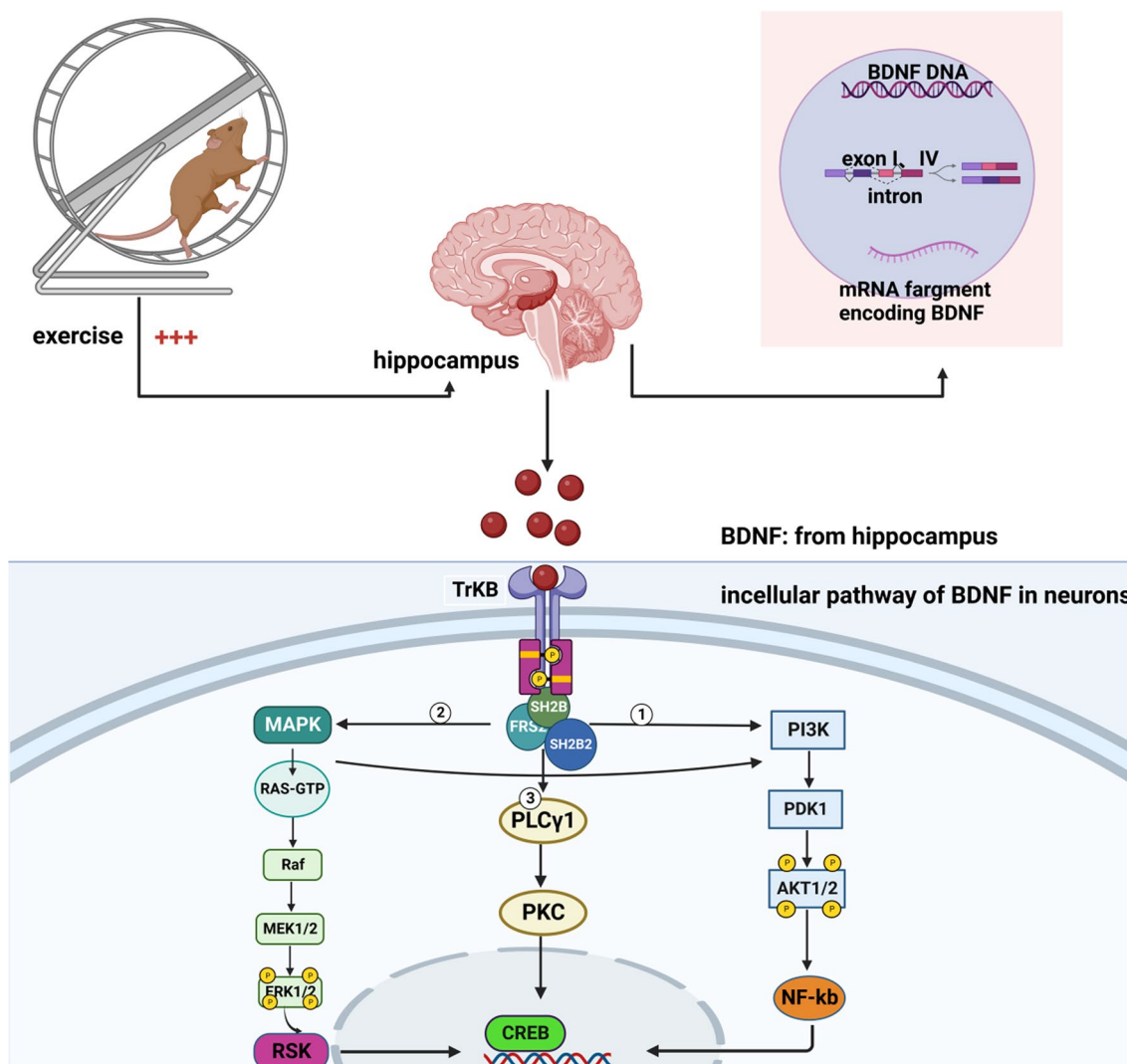


Fig. 1 Exercise improves cognitive function by promoting the production of BDNF. During exercise, the amount of BDNF mRNA exons increases, resulting in increased production of BDNF. BDNF enters the brain through the BBB and binds to the TrkB receptor on the cell membrane to activate intracellular signal transduction. ① The BDNF-TrkB complex activates the PI3K/Akt signaling pathway and regulates the survival of neurons. ② The BDNF-TrkB complex activates the MAPK/Ras/ERK signaling pathway and promotes neuronal differentiation. ③ The BDNF-TrkB complex activates the PLC- γ /PKC signaling pathway and regulates synaptic plasticity

transcription and translation of BDNF, and thus counter cognitive dysfunction through related pathways.

In addition, several studies have revealed other factors or mechanisms. For example, Martini et al. suggested that power exercise inhibits streptozotocin-induced spatial memory deficits in AD mice by activating the phosphorylation of the hippocampal BDNF/ERK/CaMKII/CREB signaling pathway [84]. Moreover, researchers have proposed that the mechanism by which exercise increases BDNF levels in brain tissue may be due to the release of an endogenous histone deacetylase (HDAC) inhibitor. Exercise induces metabolic changes in the

liver, with increased expression of the ketone body β -hydroxybutyrate (DBHB), which is synthesized from acetyl coenzyme A generated by fatty acid β -oxidation and can reach the hippocampus via the circulatory system [85]. DBHB increases the histone acetylase (HAT) and decreases the activity of HDAC in the hippocampus. Therefore, the ratio of HAT to HDAC is increased [86], resulting in reduced binding of HDAC2/3 to the BDNF promoter, which is beneficial to BDNF transcription and expression.

Although physical exercise has been associated with BDNF elevation, the relationship demonstrates a degree

of variability. A single-nucleotide polymorphism in the pro-region of the human BDNF gene, which results in a valine (Val)-to-methionine (Met) substitution called BDNF Val66Met, is considered to influence the cognitive function in degenerative diseases [87]. The polymorphism can lead to improper protein folding and reduce the binding of mature BDNF to TrkB, causing impairment in hippocampal function [88]. Meanwhile, the presence of BDNF Val66Met may influence the beneficial effects of exercise, both in humans and in mice [89–91]. For example, physical exercise is able to enhance the hippocampal-dependent memory only in the BDNF Val/Val mice (wild-type), but not in the BDNF Met/Met mice [92]. Canivet et al. observed that physically active Val/Val homozygotes have better episodic memory compared with inactive Val/Val homozygotes, while there is no difference in episodic memory between active Met carriers and inactive Met carriers [93].

Exercise improves synaptic plasticity

The neuronal synaptic network is the basis for memory formation and retention. Zhu et al. examined the synaptic proteins of excitatory synapses in all brain regions of mice by mapping whole-brain synapses. They found that the higher cognitive functions the brain regions control, the greater synaptic diversity they contain [94]. The synaptic plasticity includes presynaptic plasticity, synaptic cleft plasticity and postsynaptic plasticity, which largely depend on synaptic number and plasticity proteins, such as synaptotagmin and PSD. Synaptotagmin is a presynaptic membrane protein that is widely distributed in presynaptic vesicle membranes. The role of synaptotagmin includes regulation of synaptic vesicle transport and release of neurotransmitter [95]. Meanwhile, postsynaptic mitogens mainly include PSD-95. As a major regulator of synaptic maturation, PSD-95 can interact, stabilize and transport NMDA receptors and AMPA receptors to the postsynaptic membrane [96]. NMDA receptors and AMPA receptors are two major ionotropic receptors to selectively capture neurotransmitters in postsynaptic sites. In synapses between Schaffer collaterals and CA1 pyramidal cells in the hippocampus, exchange of glutamate receptor components, modification of receptors through phosphorylation, and addition of more receptors to the area of the postsynaptic density contribute to LTP [97]. Previous studies found that voluntary exercise or wheel running enhances LTP in the DG of young or healthy rats, probably through increase of synaptic plasticity-related proteins and membrane receptors [98, 99]. This effect of exercise on synaptic plasticity may be more evident in pathological situations. Meanwhile, in healthy individuals or AD patients, accumulation of A β alters the conformation of the C-terminal structural domain

of NMDA receptor and its interaction with the protein phosphokinase PP1 [100], leading to inhibition of excitatory synapses, LTP and neurotransmission.

Treadmill exercise leads to some morphological changes in 3 \times Tg-AD mice, including increases in synaptic number, expression of synaptotagmin, axon length, dendritic complexity, and dendritic spine number. Exercise could even restore these parameters to levels in normal control mice [101]. Meanwhile, Li et al. reported that adaptive treadmill training for 12 weeks, 5 days/week, 45 min a day, leads to improved spatial learning and memory in Tg-APP/PS1 mice, with significant increases in the number of synapses in the CA1 region of the hippocampus and in PSD expression. They concluded that exercise alleviates the impairment of postsynaptic plasticity [102]. Another exercise experiment in AD mice showed that aerobic intermittent exercise combining running with swimming for 40 min/day, 6 days/week for 4 weeks, can improve neurogenesis and cognitive behavior, possibly mediated by plasticity proteins such as synaptotagmin and PSD95 [103]. In summary, the exercise-induced morphological and functional changes of synapses in the brain significantly influence the neuronal information exchange network.

Exercise improves mitochondrial health

Mitochondria serve essential functions in neurons and mitochondrial maintenance directly affects neuronal development, function, and survival. Neurons are highly differentiated cells with a large energy demand, and therefore are highly dependent on mitochondrial function [104]. Mitochondrial damage in the brain will cause bioenergetic deficiency, intracellular calcium dysregulation and oxidative stress, leading to abnormal apoptosis of neurons. Mitochondria produce reactive oxygen species (ROS) in the process of biological oxidation and energy conversion. When there is an imbalance between the generation of ROS and the body's antioxidant defense system, oxidative stress in mitochondria would cause oxidative stress. Mitochondrial oxidative stress leads to dysregulation of the mitochondrial energy metabolism, which in turn causes damage to mitochondria, thus promoting the development of neurodegenerative disease [105]. Meanwhile, mitochondria play key roles in the development of adult neuroplasticity. For example, during early neuronal differentiation, mitochondria regulate the differentiation and growth of axons by buffering cytosolic Ca $^{2+}$ and thereby promoting polymerization of axonal microtubules [106]. Therefore, maintaining a healthy mitochondrial pool is critical to neuronal health. There are many pathways for mitochondrial quality control, such as the degradation of misfolded mitochondrial proteins, mitochondrial fission and fusion, and the

engulfment and degradation of damaged mitochondria termed mitophagy [107]. A distinctive neurobiological feature of neurodegenerative diseases is the presence of excessive oxidative stress and inflammatory responses in the brain [28], while mitochondrial functional impairment is an early pathological hallmark of neurodegenerative disease.

Exercise has been proven to promote mitochondrial biogenesis [108], maintain the balance of neuronal mitochondria, reduce excessive oxidative stress caused by mitochondrial damage, and improve ATP production [109]. Meanwhile, exercise can improve mitochondrial health in the brain by modulating mitochondrial biogenesis, kinetics (fusion/fission) and autophagy.

Mitochondrial biogenesis

Studies have demonstrated that exercise promotes mitochondrial biogenesis by inducing expression of transcription coactivator peroxisome PGC-1 α , MAPK and Sirtuin 1 (SIRT1) [75, 76]. PGC-1 α is a transcription coactivator involved in mitochondrial biogenesis and regulation of antioxidant defense [77]. Once activated through phosphorylation or de-acetylation, PGC-1 α activates nuclear respiratory factor 1/2 (NRF1/2) and subsequently mitochondrial transcription factor A (Tfam) [110]. Activation of the PGC-1 α -NRF-Tfam pathway leads to synthesis of mitochondrial DNA and proteins, and generation of new mitochondria. MAPK is an intracellular energy status sensor that maintains energy stores by regulating anabolic and catabolic pathways [78]. MAPK is activated during both exercise and muscle contraction *in vivo*, and is considered to be an important signaling molecule in the regulation of muscle metabolism during exercise and adaptation of skeletal muscle to exercise training [111]. SIRT1 may activate energy metabolism, neurogenesis and mitochondrial quality control through regulation of multiple transcription factors, including PGC-1 α . An animal study showed that 8 weeks of treadmill exercise elevated the expression of SIRT1 and PGC-1 α and reduced α -synuclein deposition levels in PD mice [112]. The exercise also increased levels of biomarkers of mitochondrial biogenesis, antioxidant enzymes, as well as key factors of mitochondrial autophagy. These results suggest that chronic aerobic exercise may increase mitochondrial biogenesis and autophagic response through SIRT1/PGC-1 α to reduce abnormal protein deposition in neurodegenerative diseases, thus improving cognitive function (Fig. 2).

Mitochondrial kinetics

Mitochondrial fusion is mainly mediated by pro-fusion proteins optical atrophy 1/2 (Opa1/2) and mitochondrial fusion protein 1/2 (mitofusin1/2, Mfn1/2), which expand the area of mitochondrial network by facilitating the

fusion of the inner and outer mitochondrial membranes (OMM). Mitochondrial fragmentation is mediated by mitochondrial fission factor and fission protein 1, which recruit dynamin-related protein 1 (Drp1) to the OMM, separating dysfunctional organelles from the mitochondrial network and allowing the isolated mitochondrial fragments to be degraded by autophagic lysosomes [30, 108]. Marques-Aleixo et al. reported that PD mice with treadmill endurance training or having free-wheel voluntary physical activity have increased expression of the fusion proteins Mfn1/2 and Opa1, and decreased expression of the cleavage protein Drp1, as measured by Western blotting [113]. These results suggest that the exercise-induced favorable alterations in mitochondrial dynamics and autophagic signaling may contribute to increased mitochondrial plasticity (Fig. 2).

Mitochondrial autophagy

Mitochondrial dysfunction causes deficient energy production, oxidative stress and impaired cell signaling, all of which are associated with the pathogenesis of cognitive dysfunction. Clearance of dysfunctional mitochondria is important for maintaining normal neuronal function [114, 115]. Following mitochondrial damage, autophagy is induced in three ways: ubiquitin-mediated mitochondrial phagocytosis, including PTEN-induced putative kinase 1 (PINK1)-Parkin (an E3 ubiquitin ligase)-dependent phagocytosis [116]; OMM receptor-mediated mitochondrial phagocytosis [117]; and lipid-mediated mitochondrial phagocytosis [118]. Exercise exerts beneficial effects in cognitive impairment diseases mainly through the first pathway. In the PINK1-Parkin pathway, PINK1 first accumulates on the OMM, which is induced by the loss of membrane potential in damaged mitochondria. The stabilized PINK1 recruits Parkin to the membrane, and then the PINK1/Parkin ubiquitinates the substrates on OMM to activate the autophagic machinery (Fig. 2) [119, 120]. A mediator of exercise that can activate the PINK1/Parkin pathway may be the nicotinamide adenine dinucleotide (NAD) [121, 122]. NAD⁺ is an important cofactor for SIRT [33]. Exercise significantly increases the intracellular NAD⁺/NADH ratio, leading to increased expression of SIRT1 in the brain [123]. The NAD⁺-SIRT1 signaling acts on mitochondrial forkhead box O (FOXO) [124], mediating FOXO1 deacetylation [125], and then activates the PINK1-Parkin pathway [126], leading to mitochondrial fission and activation of mitochondrial autophagy (Fig. 2). Furthermore, the effect of exercise in increasing NAD levels may be partly mediated through a cyclic GMP-AMP synthase (cGAS)-interferon gene stimulating hormone (STING)-dependent pathway. Hou et al. found that in APP/PS1 mutant transgenic mice, increasing NAD levels could

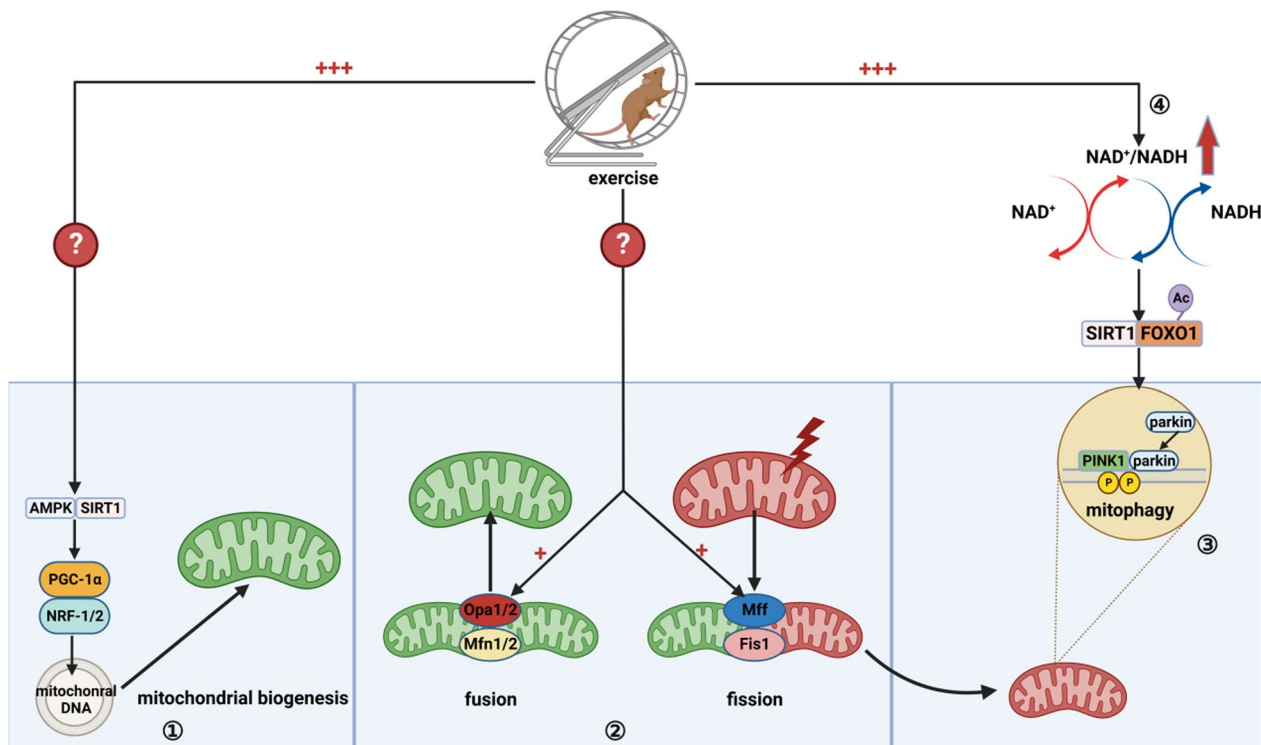


Fig. 2 Exercise benefits the stability of neuronal mitochondria and improves the oxidative stress and energy supply. ① Mitochondrial biogenesis: exercise can promote the AMPK/SIRT1/PGC-1 α pathway, recruit more NRF1/2 and then upregulate the mitochondrial gene expression. ② Fusion and fission: exercise can improve the fusion and fission proteins in mitochondria, such as Opa1/2, Mfn1/2, Mff, and Fis1. These proteins are especially important for the “metabolism” of mitochondria. ③ Mitophagy: exercise can promote the PINK/parkin pathway of mitophagy in the outer mitochondrial membrane (OMM). ④ After exercise, more NADH is converted to NAD⁺, resulting in the acetylation of FOXO1. This urges PINK1 to recruit more Parkin in the OMM to remove damaged mitochondria

reduce DNA damage. The underlying mechanisms may include decreased expression of inflammatory cytokines in the brain, decreased abnormal activation of microglia and astrocytes, and decreased activation of the CGAS–STING pathway [127].

Exercise improves cognitive function by promoting cytokine release

How does skeletal muscle come in contact with the brain? Currently, skeletal muscle is considered to be a secretory organ of the body that releases various cytokines into the circulatory system to communicate with other organs of the body [128]. Physical exercise promotes the secretion of cytokines and hormonal molecules from peripheral tissues and organs, including skeletal muscle, to act on neurons in the brain after crossing the brain–blood barrier (BBB). Then they promote the secretion of neurotrophic factors [129], reduce immune inflammatory responses, relieve stress on brain tissue, and improve synaptic plasticity and protective effects on neurons [130]. These factors mainly include irisin [131–133], clusterin (CLU) [134], and glycosylphosphatidylinositol-specific

phospholipase D1 (Gpld1, a liver-derived factor) [112, 135] (Fig. 3). They may ameliorate cognitive dysfunction through all of the above processes.

The key factor of skeletal muscle–brain axis: irisin

Irisin is released into the circulatory system by skeletal muscle during exercise. It is released on cleavage of the membrane-binding precursor protein FNDC5, which stimulates browning and thermogenesis of adipocytes [136]. Irisin is an important modulator of cognitive function under exercise therapy [137] and has the highest affinity for $\alpha v/\beta 5$ integrin in skeletal muscle [138]. FNDC5/irisin is highly sensitive to exercise stimuli. Recent studies have identified that exercise may improve cognitive function through FNDC5/Irisin [139, 140]. For example, boosting brain FNDC5/irisin levels can rescue synaptic plasticity and memory defects in a mouse model of AD [141]. Islam et al. found that genetic deletion of FNDC5/irisin (global FNDC5 knock-out (KO) mice; F5KO) impairs cognitive function in exercise, aging and AD [137]. The diminished pattern separation in F5KO mice can be rescued by delivering Irisin directly into the

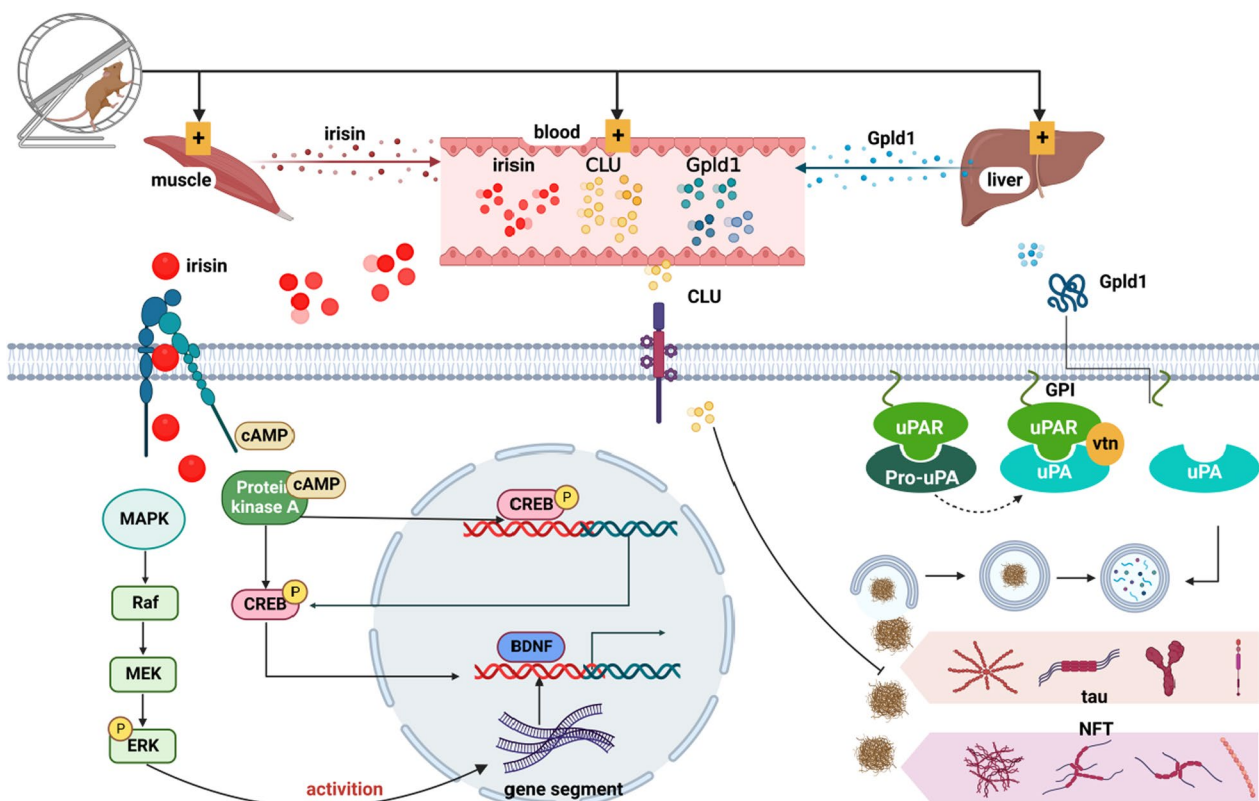


Fig. 3 Exercise can stimulate various organs in the body to secrete corresponding cytokines. Muscle: after exercise, skeletal muscle secretes a large amount of Irisin into the peripheral system. Irisin is internalized into cells by binding to integrin receptors and passes through the blood–brain barrier, activating the MAPK/ERK and cAMP/CREB pathways and promoting the production of BDNF. Liver: exercise stimulates the liver to secrete Gpld1 into the blood, a specific phospholipase that can reduce amyloid precipitation anchored by GPI on the neuronal cell membrane. Blood: exercise enhances the level of clusterin (CLU). LRP8, a special receptor in the brain, mediates the entry of CLU into the cytoplasm. CLU can inhibit A β aggregation and neurofibrillary tangles

DG. In addition, the F5KO mice receiving voluntary free-wheel exercise fails to show exercise-induced improvements in spatial learning and memory in comparison to the WT mice with the same amount of exercise. Furthermore, in F5KO mice, adult-born neurons in the DG showed abnormal morphology, transcription, and function [137].

Irisin reaches the CNS through the BBB after exercise and activates the MAPK/ERK and cAMP/protein kinase A (PKA)/CREB signaling pathways, resulting in increased expression of BDNF in neurons (Fig. 3). Li et al. found that irisin treatment increases the levels of phosphorylated Akt and ERK1/2 in middle cerebral artery occlusion mice. When ERK1/2 expression was blocked by specific inhibitors, the neuroprotective effect of irisin disappeared. These results suggest that irisin may exert its neuroprotective effect through the MAPK/ERK signaling pathway (Fig. 3) [142]. Phosphorylation of MAPK/ERK activates the induction of a large number of activity-regulated genes related to cognition in the nucleus, such as *Arc/Arg3.1*, *Arl5b*, *Gadd45b*, *Homer1*, *Inhba*,

and *Zwint* [143]. Activity-dependent gene expression is important for the formation and maturation of neuronal networks, neuronal survival, and plastic modifications within mature networks [144]. The phosphorylation of MAPK/ERK initiates the transcriptional process in the hippocampus (Fig. 3) [145]. Sun et al. performed treadmill training on AD model mice injected with A β in the hippocampus, and found that physical exercise prevented A β -induced cognitive deficits in object recognition tasks and Morris water maze. Further studies showed that exercise regulated neurogenesis and brain immune activity by altering ERK modifications and controlling MAPK/ERK signaling pathways [146].

A recent study found that recombinant Irisin stimulates the cAMP/PKA/CREB pathway in cortical slices of AD mice [141]. This pathway has been shown to inhibit the transcription and expression of endogenous tau protein, which is thought to be involved in the molecular mechanism regulating cognitive dysfunction, modulating neuroplasticity, and preventing memory dysfunction [147]. The Irisin-induced CREB

phosphorylation can be abolished after application of PKA inhibitor, myristoylated PKI 14–22 [141]. Exercise can promote peripheral cAMP and CREB levels in mice. As an intracellular second messenger, cAMP undergoes conformational change upon binding to the regulatory subunit of PKA, leading to release of the catalytic subunit and phosphorylation of the substrate of cAMP, thereby promoting the release of neurotransmitters from synaptic connections between neurons. In contrast, CREB, the DNA transcription-binding factor of BDNF, can promote neurogenesis by increasing the activity of RNA polymerase of BDNF to regulate the expression of BDNF gene in the hippocampus (Fig. 3) [148]. Lee et al. reported that short-term memory of cerebral ischemic mice was improved after treadmill exercise. Further molecular evidence showed increased phosphorylation of the Akt-CREB-BDNF pathway and decreased neuronal apoptosis in the hippocampus [149]. Ko et al. found that treadmill training for 8 weeks inhibited phosphorylation of CREB in the hippocampus and increased the CREB/p-CREB ratio in mice with traumatic brain injury (TBI). These results suggest that treadmill exercise improves spatial learning by improving the CREB/BDNF/TrkB signaling pathway in TBI mice [150].

Other cytokines in the skeletal muscle-brain axis

Recently, more and more cytokines are being found in the crosstalk between skeletal muscle and brain. Cathepsin B (CTSB), a muscle secretory factor, is important for the cognitive and neurogenic benefits of running. Moon et al. have found that running increases CTSB levels in mouse gastrocnemius muscle and plasma. Furthermore, application of recombinant CTSB enhances the expression of BDNF and doublecortin (DCX) in adult hippocampal progenitor cells through a mechanism dependent on the multifunctional protein P11. The findings suggest that CTSB is a mediator of effects of exercise on cognition in the skeletal muscle-brain axis [151]. Exercise-induced apelin is demonstrated to be beneficial to sarcopenia. Recently, evidence shows that apelin-13, an active form of apelin, suppresses neuroinflammation and improves cognitive decline in diverse pathological processes. An animal study found that apelin-13 may upregulate the glucocorticoid receptor level and nuclear translocation in hippocampus [152]. Moreover, kynurenine accumulation can be suppressed by activating kynurenine clearance in skeletal muscle after exercise, benefiting the brain. Cervenka et al. have discussed peripheral mechanisms of tryptophan-kynurenine metabolism and their effects

on inflammatory, metabolic, and psychiatric disorders [153].

CLU

Physical exercise is generally beneficial against cognition decline, which is associated with reduced inflammation in the hippocampus. Yet, little is known about the mechanisms. CLU, also known as apolipoprotein J, is a multifunctional glycoprotein present in plasma [154]. CLU expression is near-ubiquitous, and CLU mRNA is found in almost all cell types. CLU expression is increased in response to a broad variety of signals and conditions, including the presence of oncogenes, numerous growth factors and cytokines, as well as many stress- or apoptosis-inducing conditions/agents such as heat shock, UVA, UVB, proteotoxic stress, heavy metals, oxidants, hypoxia, ionizing radiation, and chemotherapeutic drugs [44]. Recently, a study found that injecting the 'exercise plasma' collected from voluntarily running mice into the sedentary mice induces reductions in baseline expression of neuroinflammatory genes and experimentally induced brain inflammation [155]. The authors also performed a proteomic analysis of the plasma composition in exercising mice and found that the levels of specific cytokines, such as CLU, glycoprotein pigment epithelium-derived factor (PEDF), and leukemia inhibitory factor receptor (LIFR), are increased after exercise [155]. When mice were further injected with exercise plasma without CLU, PEDF, or LIFR, the gene expression and protein levels of anti-inflammatory factors were significantly reduced in the CLU-deficient mice. Moreover, the researchers found increased plasma CLU levels as well as improved cognition and memory in patients with MCI after 6 months of physical activity intervention [155]. LRP8, also known as APOER2, is the receptor of CLU [156] and expressed most highly in brain endothelial cells and neurons [155]. This indicates that elevated CLU in blood may bind to brain endothelial cells through LRP8 receptors and benefit the brain. Protein aggregation is a common pathological hallmark across neurodegenerative diseases. Similar to CLU co-localizing with A β in the senile plaques, in the case of α -synucleinopathies, CLU co-localizes with cortical Lewy bodies in the brain. Moreover, the co-expression of CLU may protect neurons from proteotoxicity [157]. In mice injected intravenously with recombinant clusterin (rCLU) labelled with Atto-647 N fluorophore, researchers found a prominent decoration of the cerebrovasculature of the hippocampus with Atto-647 N-rCLU [155], which demonstrated that endothelial cells and neurons may be the immediate target of circulatory CLU.

Besides anti-neuroinflammation, researchers have also summarized the effects of CLU on AD, including A β aggregation and clearance [158], neurofibrillary

tangle and tau protein phosphorylation [159]. de Retana et al. treated 14-month-old APP23 transgenic mice with subchronic intravenous CLU for 1 month and measured the concentration and distribution of A β in the brain, as well as the levels of A β in plasma and cerebrospinal fluid after treatment. The results showed that CLU treatment prevented the accumulation of A β in cerebral arteries and induced a reduction of total brain insoluble A β [160]. Wojtas et al. found that CLU has a significant effect on anxiety-like behavior in the context of tau pathology, as manifested in the open field test and elevated plus maze [159]. In vitro studies found that CLU significantly inhibits tau protein fibrillation and neurofibrillary tangle formation. Down-regulation of CLU leads to increased α -synuclein aggregation in SH-SY5Y cells stably over-expressing α -synuclein [161], which may exacerbate the course of cognitive impairment of PD. These studies illustrate the beneficial role of CLU in improving cognitive dysfunction during ageing or in neurodegenerative diseases. Therefore, CLU may be one of the important mediators of the effects of exercise on the CNS.

The liver-brain axis: Gpld1

Gpld1 is a phospholipase that can cleave important proteins fixed to the cell membrane via glycosylphosphatidylinositol (GPI). The lysed proteins are released from the cell surface to perform different biological functions (Fig. 3) [162]. Previous studies have found that Gpld1 plays a beneficial role in the pathological processes of chronic diseases, such as chronic liver disease, diabetes and cancer, by cleaving proteins such as triglycerides [163], proteoglycans [164], and carcinoembryonic antigen [165].

In a recent animal study by Horowitz et al., researchers found that systematic blood plasma administration can transfer the benefits of exercise to the aged hippocampus. The levels of BDNF and neurogenesis increase in the hippocampus, and the number of mature neurons expressing 5-bromo-2'-deoxyuridine and Dcx increases significantly. Furthermore, the ability of mice to perform radial arm water maze (RAWM) and novel object recognition tasks is also improved, suggesting improvement of the cognitive ability of elderly mice [112]. The authors also sought to identify individual circulating blood factors that mediate these effects. They used isobaric tagging together with liquid chromatography-tandem mass spectrometry to measure relative amounts of soluble proteins in the plasma, and found that 63% and 67% of exercise-induced factors in aged and mature mice, respectively, are predominantly expressed in the liver, in which Gpld1 and paraoxonase 1 are overrepresented [112]. The increased Gpld1 concentrations in plasma are correlated with improved cognitive performance in the

RAWM and contextual fear conditioning behavioral test in aged mice [112].

Mechanistic studies suggest that exercise may improve age-related regeneration and cognitive impairment by altering the expression of related proteins in the urokinase-type plasminogen activator receptor (uPAR) signaling pathway downstream of GPI anchored substrate cleavage (41 coagulation and complement proteins in the uPAR signaling pathway were found to be reduced after exercise) [112]. The study suggested that Gpld1 may be one of the key cytokines acting in the muscle-brain axis, but more in-depth studies are still needed to validate the underlying molecular mechanism.

In addition to the cytokines mentioned above, recent studies have also found that the proteasomal adaptive response induced by skeletal muscle stress is also important for protein quality control in the brain, reducing age-related proteasomal substrate accumulation [166]. NADPH oxidase also protects against ageing and oxidative stress in the brain. A recent study found a biological mechanism by which liver metabolites regulate synaptic activity in the prefrontal cortex by enhancing synaptic related RNA methylation in the brain after exercise, thus preventing the occurrence of anxiety-like phenotypes [167].

The link between exercise and specific cytokines is gradually being explored and validated. In summary, exercise can act as a stimulator for body organs, including skeletal muscle, allowing secretion of specific factors that act on brain tissue.

Exercise improves cognitive function by improving brain metabolism

Glucose is the main energy supplier in the brain, while ketone bodies and lactate provide a small proportion of energy. Healthy energy metabolism is beneficial to cognitive function. Glucose plays an important role in a variety of neurological processes such as the synthesis and recycling of neurotransmitters, and influences processes of message transmission and synaptic remodeling [33]. Dysfunctional glucose metabolism is present in brain regions of patients with neurodegenerative diseases. For example, in the hippocampus, hypothalamus, striatum and insular cortex of patients with AD, the glucose metabolism is reduced [168]. Therefore, these regions are considered to be characteristic areas of AD pathogenesis [168].

Glucose metabolism

Glucose utilization in brain tissue mainly includes glucose transport and intracellular glucose catabolism. It has been hypothesized that various pathogenic cascades caused by impaired glucose metabolism in brain may lead to neuronal degeneration, thus leading to

cognitive dysfunction [169]. Glucose is transported to various types of brain cells mainly through glucose transporters (GLUTs), of which GLUT1 is mainly distributed in the BBB endothelial cells and GLUT3 is concentrated in neuronal axons and dendrites. Both are important pathways that mediate neuronal glucose uptake (Fig. 4) [170]. A recent study showed that regular exercise enhances the expression of GLUT1 and GLUT3 in the CNS and improves spatial learning and exploration as assessed by the Morris water maze test in AD model mice [171]. Similarly, exercise also improves glucose metabolism by inhibiting HDAC4 and upregulating GLUT1 expression. This effect may be achieved by increasing glycolysis, respiratory function, and ATP production (Fig. 4) [172].

Insulin resistance

Insulin resistance is often present in brains of CNS disorders, resulting in an energy deficit in the brain that suffers from oxidative and metabolic damage [173]. A recent study showed that exercise promotes insulin to cross the BBB into brain tissue and improves its binding to blood vessels in the mouse brain [174]. Insulin/PI3k/Akt is an important signaling pathway for insulin transmission in the brain, maintaining glucose homeostasis and metabolism [175]. Exercise can inhibit downstream activation of glycogen synthase kinase-3β (GSK-3β) by reducing insulin resistance in the brain and activating the PI3K/Akt pathway [146, 176]. GSK-3β is a key factor causing abnormal protein aggregation and NFTs in the brain, which can lead to the disruption of neuronal function and synaptic damage [177]. The presence of excess GSK-3β in brain tissue can cause irreversible impairment of cognitive

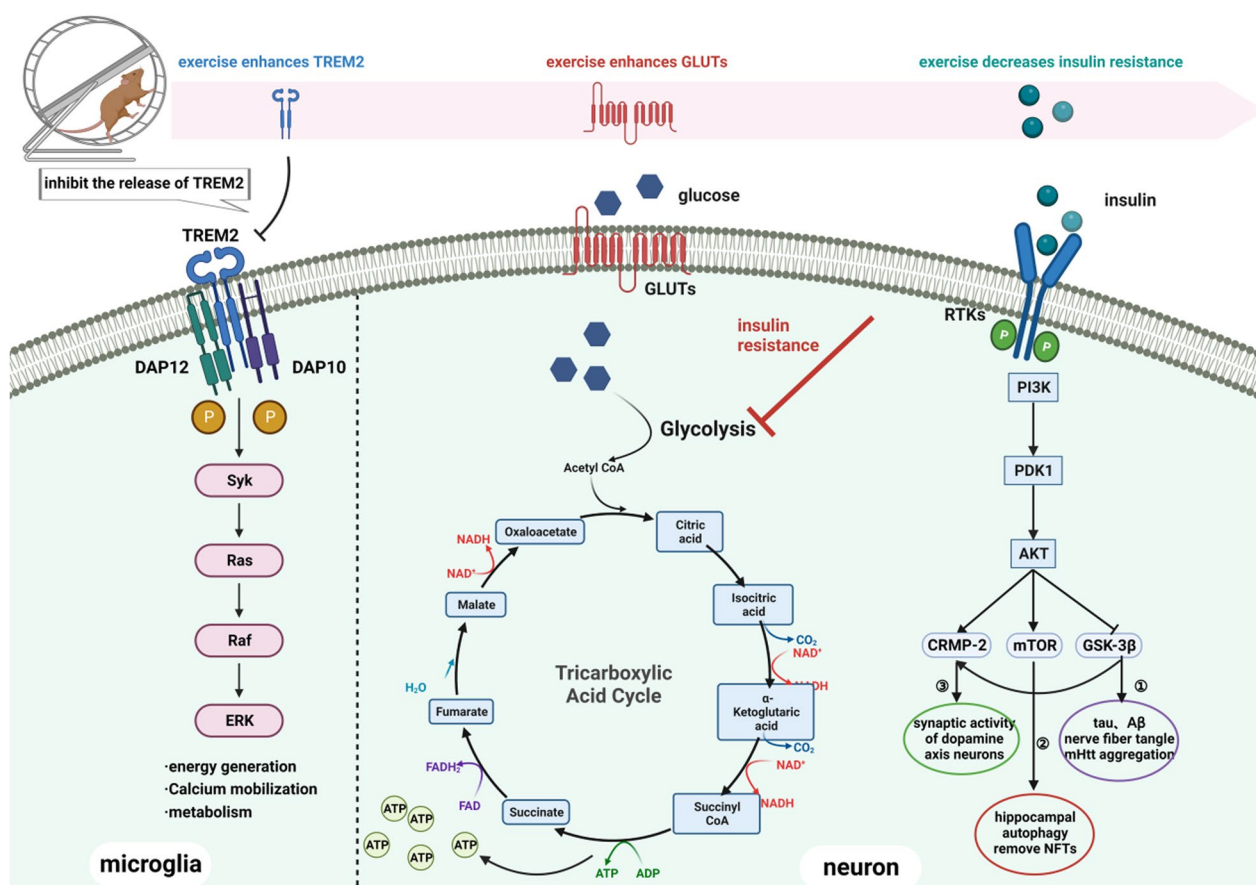


Fig. 4 Exercise can improve the energy metabolism of the brain, which is beneficial to cognitive function. Insulin resistance: exercise reduces insulin resistance in the brain, allowing more insulin to reach the brain through the blood–brain barrier. Activation of the PI3K/Akt pathway can lead to activation of mTOR and CRMP-2 as well as inhibition of GSK3β, resulting in ① decreased deposition of Tau and Aβ proteins, neurofibrillary tangles (NFTs), and aggregation of mHtt; ② activation of hippocampal autophagy and clearance of NFTs; and ③ improved synaptic activity of dopaminergic neurons. Glucose metabolism: exercise increases the amount of GLUTs that can remove more glucose to the cytoplasm. Glucose undergoes glycolysis and the tricarboxylic acid cycle to provide more ATP to brain tissue. Microglia: TREM2, by binding to DAP10/12, promotes Syk phosphorylation and regulates metabolic processes, including energy generation, calcium mobilization and brain metabolism

function. GSK-3 is now considered as an early biomarker of AD (Fig. 4) [178]. In addition, in HD, neurotoxicity is attenuated by GSK-3 β inhibitors. Inhibition of GSK-3 β activates mitochondrial lysosomes, leading to timely clearance of toxic aggregates of mutant Huntingtin [179]. In PD, collapsed response mediator protein 2 (CRMP-2), a downstream signal factor of PI3K/Akt/GSK-3 β , regulates the degeneration of axons and dendrites of dopaminergic neurons through microassembly [180]. It may also be one of the possible mechanisms by which exercise improves PD cognitive function. Studies have demonstrated that swimming exercise activates PI3K/Akt, resulting in reduced phosphorylation of GSK-3 β and increased phosphorylation of CRMP-2, reducing the vulnerability to stress and mediating neuroplasticity in mice (Fig. 4) [146].

As a physiological stimulus, physical exercise can also promote glucose uptake and energy metabolism through activation of AMPK [181] and mammalian target of rapamycin (mTOR) (Fig. 4) [182]. Zheng et al. found that the PI3K/Akt/mTOR signaling pathway plays a role in regulating hippocampal autophagy and removing NFTs [183]. Meanwhile, Kang et al. found that treadmill exercise produces beneficial effects on PI3K/Akt/mTOR, autophagy and tau protein hyperphosphorylation in the cerebral cortex of NSE/hTau23 transgenic mice [182]. Both experiments eventually observed improvements of cognitive function in mice.

Microglia

Glucose metabolism in microglia is also important for maintaining normal cognitive function of the brain [184]. Piers et al. found significant metabolic abnormalities in the microglia of AD patients with myeloid 2 (TREM2) gene variants, which included a failure of the glycolytic immunometabolic switch [185]. Microglia also play a key role in the elimination of abnormal protein aggregation in the brain in neurodegenerative diseases [186]. TREM2 is a cell-surface transmembrane glycoprotein that is highly expressed in microglia [187]. It can mediate intracellular signaling by binding to the DNAX activating protein 12/10, and plays a role in promoting SYK (Tyr525/526) phosphorylation, regulating calcium mobilization, mTOR signaling pathway, AMPK signaling pathway, etc. (Fig. 4) [188]. TREM2 is also necessary for microglia-related regulation of synaptic plasticity and participates in the communication between microglia and other cells. AD mice with knockout of *Trem2* at late stage (6–10 months) show accelerated synaptic dysfunction because of more severe amyloid deposition caused by depression of microglia phagocytosis [189]. Evidence shows that TREM2 responds to extracellular signals, such as IL-1 β , TNF- α , ROS, and even solute TREM2 (sTREM2), and increases

the secreta of microglia, that regulate synaptic plasticity [190].

Recent studies believe that microglia are involved in the improvement of synaptic plasticity through the TREM2 pathway after running exercise. In APP/PS1 AD mice, microglial number, protrusion length and endpoints are increased after long-term voluntary exercise, together with increased protein levels of GLUT5, TREM2, and phosphorylated SYK. The authors found more TREM2-positive fluorescent labels in the microglia of AD-Running mice. In addition, the levels of TREM2 in the hippocampus are significantly increased, while sTREM2 in the plasma is significantly reduced in AD-Running mice compared with AD-Sedentary mice. These results indicate that running exercise upregulates the TREM2 protein in the hippocampus, reduces TREM2 shedding and prevents sTREM2 release into the blood in APP/PS1 mice [191]. In summary, inhibiting the loss of TREM2 may be one of the mechanisms by which running exercise improves glucose metabolism in the hippocampus and rescues cognitive decline in APP/PS1 mice.

Exercise improves cognition through regulation of gut microflora

Neurodegenerative diseases are often accompanied by dysbiosis of the gut flora [136] and disruption of intestinal barrier [192]. An unhealthy gut can cause abnormal neuroinflammation and oxidative stress. Some products of intestinal flora are also involved in the pathology of abnormal protein aggregation in cognitive dysfunction [193, 194].

The modulator between gut and brain: *Akkermansia muciniphila*

Akkermansia muciniphila (AKK) is considered to be a genus of bacteria that produces beneficial effects in neurodegenerative diseases. It is observed that the abundance of AKK decreases during the pathological process of cognitive disorders. EranBlacher et al. injected 11 different symbiotic bacteria into amyotrophic lateral sclerosis mice to explore their association with the severity of cognitive impairment. They found that cognitive function is improved in mice injected with AKK [195]. Meanwhile, Laura et al. observed a compensatory increase in AKK during the early course of progressive MS, which shows a negative correlation with the symptoms of disability [196]. Ou et al. demonstrated the protective role of AKK against cognitive deficits and amyloid pathology in a mouse model of AD. The ameliorative effect of AKK treatment on cognitive function can be attributed to the repair of metabolic disorders and, concomitantly, reduction of A β pathology [197].

In a recent study, APP/PS1 AD model mice and WT mice performed treadmill exercise for 45 min per day, 5 days a week, for 8 weeks with gradual increase of load period and 4 weeks with a constant load period. The results showed that treadmill exercise enriched the intestinal microbial community composition in AD-exercise mice compared with AD-sedentary [198]. Furthermore, the dominant species in the AD-exercise group were *Bacteria*, *Verrucomicrobiota*, *Verrucomicrobiae*, *Verrucomicrobiales*, *Akkermansiaceae*, and *Akkermansia*. In the review of the previously reported effect of AKK on intestinal mucosal [199, 200], the authors speculate that treadmill exercise can protect the intestinal barrier and provide beneficial effects on the brain by increasing AKK abundance [198].

The intestinal barrier

Neurodegenerative diseases are often accompanied by inhibition of tight junction protein gene expression and decreased levels of tight junction proteins ZO-1, Occludin, and Claudin. The intestinal epithelium is damaged, microvilli are sparse, and paracellular space is widened, resulting in increased intestinal permeability. When the intestinal barrier and BBB are disrupted, products of the intestinal flora, such as lipopolysaccharide (LPS) [201] and amyloid [202], would leak through the barrier into brain tissue, leading to activation of inflammatory response, neuronal apoptosis and abnormal protein deposition in the brain (Fig. 5). Studies have confirmed that LPS in the brain will activate the Toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/nuclear factor kappaB (NF- κ B) signaling pathway in neurons [203], causing elevated expression of MyD88, p-I κ B- α and NF- κ B and decreased expression of I κ B- α (Fig. 5). As a transcription factor downstream of the TLR4/MyD88 pathway, NF- κ B can stimulate the change of microglia from phenotype M1 to M2. M2 microglia, also known as amoeboid microglia, have an anti-inflammatory and neuroprotective function, which produce anti-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and thereby activate the expression of iNOS and COX2 (Fig. 5). Ning et al. used intraperitoneal injection of LPS to observe the induction of neuroinflammation and apoptosis in mice. The results showed that the levels of TNF- α , IL-1 β , MDA and ROS in brain tissue increased 8 h after administration, and the numbers of neurons in CA1, CA3, and cerebral cortex were decreased (Fig. 5) [204].

Physical exercise exerts neuroprotective effects probably by maintaining a normal intestinal mucosa and intestinal barrier. Campbell and colleagues reported that 12 weeks of voluntary wheel running improves intestinal epithelial membrane integrity, reduces intestinal

inflammation, and increases microbial diversity in mice [201]. In a recent study, Shin et al. found that 4 weeks of treadmill exercise (12 m/min for 30 min/day in week one, with an increase of 2 m/min every week) results in increased expression of the tight junction proteins claudin-1 and occludin, and decreased serum level of LPS in C57BL/6J mice, as detected by Western blotting. The result suggests that plate exercise can increase the expression of tight junction proteins in aged mice, protect the permeability of the intestinal barrier and maintain a stable intestinal environment [205]. Therefore, it can be concluded that exercise plays a role in maintaining both intestinal flora and intestinal barrier stability and has beneficial effects on cognition through the gut-brain axis.

Conclusion

The molecular mechanisms underlying the effects of exercise on cognition are complex. Undoubtedly, brain plasticity is the direct target for exercise. In general, in both healthy individuals and patients with degenerative diseases, exercise can enhance brain plasticity through neurotrophic factors and synaptic plasticity. Neurotrophic factors nourish neurogenesis, as well as improving neuronal survival and regeneration in various regions, while synaptic plasticity is the basis for information transmission. For example, in mouse and human studies, the increase of hippocampal level of BDNF caused by exercise is proven to improve cognitive function; after exercise, both the increase of hippocampal volume and the expression of synaptic plasticity proteins will enhance LTP; and some studies have addressed the effect of exercise on adult neurogenesis, dendritic remodeling, and cognition. Mitochondria serve essential functions in neurons and mitochondrial maintenance directly affects neuronal development, function, and survival. Exercise maintains the stability of mitochondrial quantity and quality to some extent, improving the brain's oxidative stress state and reducing the production of pro-inflammatory factors by microglia. Proteins involved in neuronal mitochondrial biogenesis, kinetics and autophagy, such as fusion proteins, cleavage proteins and proteins in the PINK1–Parkin pathway, may mediate the effects of exercise on neuronal mitochondria. Meanwhile, energy metabolism is critical to neuronal activity. Exercise maintains metabolism by reducing insulin resistance and increasing levels of GLUTs in the brain, providing energy basis for neuron activity.

The muscle-brain axis, the gut-brain axis and the liver-brain axis have been the focus and a hotspot in research of the mechanisms underlying exercise improvement of cognitive function in recent years. For example, the link between gut flora and brain cognition has now been

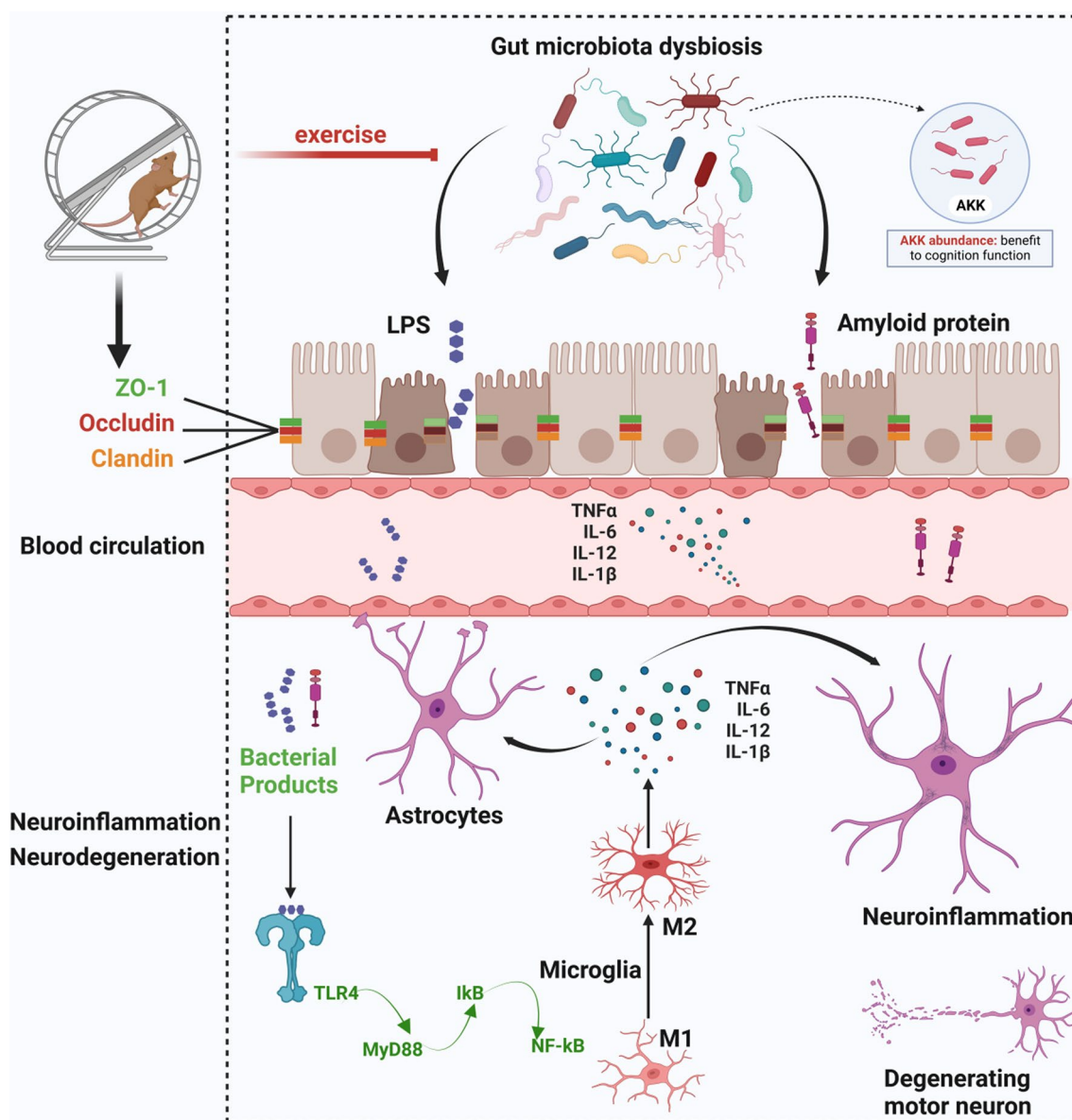


Fig. 5 Exercise improves cognitive function through the gut-brain axis. In the context of disrupted intestinal barrier, LPS and amyloid proteins may enter the brain. LPS activates aberrant polarization of astrocytes via TLR4/MyD88/IκB/NF-κB and produces large amounts of pro-inflammatory factors. This is immediately followed by microglia-mediated neuroinflammation and degeneration of motor neurons, ultimately leading to cognitive dysfunction. Exercise improves the integrity of the intestinal epithelium and increases the levels of tight junction proteins, such as ZO-1, Occludin, and Claudin. A stronger intestinal barrier reduces the entry of LPS and amyloid into the brain, and attenuates the above reactions within the brain

continuously investigated. Fecal colony transplantation in aged mice with neurodegenerative diseases improves cognitive function, and the increase in AKK after exercise plays a role in cognitive improvement. However, other potentially beneficial or harmful gut flora and their products are still needed to be explored. Organs such as the liver and skeletal muscle have also attracted attention, as they have been demonstrated to produce factors that are involved in various physiological processes in the brain to

maintain healthy cognitive function or inhibit pathological processes of various neurodegenerative diseases, ultimately delaying cognitive decline.

In the context of cognitive impairment in neurodegenerative diseases, there is often an abnormal accumulation of proteins. Excessive oxidative stress, energy metabolism disorder and neuroinflammation in the brain will aggravate this process. Therefore, exercise can not only improve neural plasticity, but also alleviate this abnormal

pathological state. However, the effects may vary with individual genetic characteristics, disease type, exercise type, etc.

The pathways from exercise to cognitive function in the brain are vast and complex. Although significant progresses on molecular mechanisms have been made in recent years, more studies in greater depth are still needed. A full understanding of the mechanisms linking exercise to cognitive function can facilitate improvement of cognitive function in the elderly population, maintenance of the healthy cognitive status in the normal population, and development of drugs for cognitive function improvement.

Abbreviations

MCI	Mild cognition impairment
MS	Multiple sclerosis
PD	Parkinson disease
NFT	Neurofibrillary tangle
BDNF	Brain-derived neurotrophic factor
CREB	CAMP-response element binding protein
PKC	Protein kinase C
TNF- α	Tumor necrosis factor- α
IL-1 β	Interleukin-1 β
QNP	Quiescent neural progenitor
INP	Intermediate neural progenitor
AHN	Adult hippocampus neurogenesis
LTP	Long-term potentiation
HD	Huntington disease
PGC-1 α	Proliferator-activated receptor gamma co-activator 1- α
FNDC5	Fibronectin type III domain protein 5
TrkB	Tropomyosin-related kinase B
PI3K	Phosphatidylinositol 3-kinase
MAPK	Mitogen-activated protein kinase
PLC γ	Phospholipase C γ
Akt	Protein kinase B
ERK	Extracellular signal-regulated protein kinase
BACE1	Beta-amyloid precursor protein cleaving enzyme 1
HDAC	Histone deacetylase
HAT	Histone acetylase
SIRT1	Sirtuin 1
NRF1/2	Nuclear respiratory factor 1/2
Tfam	Transcription factor A
Opa1/2	Optical atrophy 1/2
Mfn1/2	Mitofusin1/2
OMM	Outer mitochondrial membranes
Drp1	Dynamin-related protein 1
PINK1	PTEN-induced putative kinase 1
NAD	Nicotinamide adenine dinucleotide
PKA	Protein kinase A
TBI	Traumatic brain injury
PEDF	Pigment epithelium-derived factor
LIFR	Leukemia inhibitory factor receptor
CTSB	Cathepsin B
Gpld1	Glycosylphosphatidylinositol-specific phospholipase D1
GPI	Glycosylphosphatidylinositol
GLUT	Glucose transporter
GSK-3 β	Glycogen synthase kinase-3 β
mTOR	Mammalian target of rapamycin
TREM2	Myeloid 2
AKK	<i>Akkermansia muciniphila</i>
LPS	Lipopolysaccharide
TLR4	Toll-like receptor 4
MyD88	Myeloid differentiation primary response 88
NF- κ B	Nuclear factor kappaB

Acknowledgement

Not applicable.

Authors contributions

Yi Lu and Faqian Bu: conceptualization, methodology, software, data curation, and original draft preparation. Fang Wang, Li Liu and Shuai Zhang: visualization and investigation. Xiuying Hu and Guan Wang: supervision. Guan Wang: writing, reviewing and editing. All authors read and approved the final manuscript document.

Funding

This work was supported by the National Natural Science Foundation of China (22177083), West China Nursing Discipline Development Special Fund Project, Sichuan University (HXHL21011, HXHL20015), and Sichuan Science and Technology Program (2022NSFSC1290, 2022NSFSC1393, and 2021YJ0016).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing Interests

The authors have declared that no competing interest exists.

Received: 23 September 2022 Accepted: 9 February 2023

Published online: 27 February 2023

References

- Petersen RC, Lopez O, Armstrong MJ, Getchius T, Ganguli M, Gloss D, et al. Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:126–35.
- Montine TJ, Bukhari SA, White LR. Cognitive impairment in older adults and therapeutic strategies. *Pharmacol Rev*. 2021;73:152–62.
- Chan KY, Wang W, Wu JJ, Liu L, Theodoratou E, Car J, et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990–2010: a systematic review and analysis. *Lancet*. 2013;381:2016–23.
- Lopez OL, Kuller LH. Epidemiology of aging and associated cognitive disorders: Prevalence and incidence of Alzheimer's disease and other dementias. *Handb Clin Neurol*. 2019;167:139–48.
- Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's Dement*. 2013;9:63–75.
- Maresova P, Mohelska H, Dolejs J, Kuca K. Socio-economic aspects of Alzheimer's Disease. *Curr Alzheimer Res*. 2015;12:903–11.
- Benedict R, Amato MP, DeLuca J, Geurts J. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *Lancet Neurol*. 2020;19:860–71.
- Baiano C, Barone P, Trojano L, Santangelo G. Prevalence and clinical aspects of mild cognitive impairment in Parkinson's disease: a meta-analysis. *Mov Disord*. 2020;35:45–54.
- Knierim JJ. The hippocampus. *Curr Biol*. 2015;25:R1116–21.
- Burke SN, Barnes CA. Neural plasticity in the ageing brain. *Nat Rev Neurosci*. 2006;7:30–40.
- Ashrafi H, Zadeh EH, Khan RH. Review on Alzheimer's disease: inhibition of amyloid beta and tau tangle formation. *Int J Biol Macromol*. 2021;167:382–94.

12. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray CK, et al. Author correction: Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers*. 2021;7:53.
13. Palermo G, Del PE, Bonuccelli U, Ceravolo R. Early autonomic and cognitive dysfunction in PD, DLB and MSA: blurring the boundaries between alpha-synucleinopathies. *J Neurol*. 2020;267:3444–56.
14. Anderson ND. State of the science on mild cognitive impairment (MCI). *CNS Spectr*. 2019;24:78–87.
15. Teleanu DM, Niculescu AG, Lungu II, Radu CI, Vladacenco O, Roza E, et al. An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. *Int J Mol Sci*. 2022;23:5938.
16. Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, et al. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: a meta-analysis of in vivo magnetic resonance spectroscopy studies. *Ageing Res Rev*. 2021;72:101503.
17. Cui MY, Lin Y, Sheng JY, Zhang X, Cui RJ. Exercise intervention associated with cognitive improvement in Alzheimer's disease. *Neural Plast*. 2018;2018:9234105.
18. Siddappaji KK, Gopal S. Molecular mechanisms in Alzheimer's disease and the impact of physical exercise with advancements in therapeutic approaches. *AIMS Neurosci*. 2021;8:357–89.
19. Fari G, Lunetti P, Pignatelli G, Raelle MV, Cera A, Mintrone G, et al. The effect of physical exercise on cognitive impairment in neurodegenerative disease: from pathophysiology to clinical and rehabilitative aspects. *Int J Mol Sci*. 2021;22:11632.
20. Gallardo-Gomez D, Del PJ, Noetel M, Alvarez-Barbosa F, Alfonso-Rosa RM, Del PCB. Optimal dose and type of exercise to improve cognitive function in older adults: a systematic review and bayesian model-based network meta-analysis of RCTs. *Ageing Res Rev*. 2022;76: 101591.
21. Turner DT, Hu MX, Generaal E, Bos D, Ikram MK, Heshmatollah A, et al. Physical exercise interventions targeting cognitive functioning and the cognitive domains in nondementia samples: a systematic review of meta-analyses. *J Geriatr Psychiatry Neurol*. 2021;34:91–101.
22. Huang X, Zhao X, Li B, Cai Y, Zhang S, Wan Q, et al. Comparative efficacy of various exercise interventions on cognitive function in patients with mild cognitive impairment or dementia: a systematic review and network meta-analysis. *J Sport Health Sci*. 2022;11:212–23.
23. Vilela TC, Muller AP, Damiani AP, Macan TP, Da SS, Canteiro PB, et al. Strength and aerobic exercises improve spatial memory in aging rats through stimulating distinct neuroplasticity mechanisms. *Mol Neurobiol*. 2017;54:7928–37.
24. Paolucci EM, Loukov D, Bowdish D, Heisz JJ. Exercise reduces depression and inflammation but intensity matters. *Biol Psychol*. 2018;133:79–84.
25. Danese E, Lippi G, Sanchis-Gomar F, Brocco G, Rizzo M, Banach M, et al. Physical exercise and DNA injury: good or evil? *Adv Clin Chem*. 2017;81:193–230.
26. Sanguesa G, Battlle M, Munoz-Moreno E, Soria G, Alcarraz A, Rubies C, et al. Intense long-term training impairs brain health compared with moderate exercise: Experimental evidence and mechanisms. *Ann NY Acad Sci*. 2022;1518:282–98.
27. Coelho FG, Gobbi S, Andreatto CA, Corazza DI, Pedroso RV, Santos-Galduroz RF. Physical exercise modulates peripheral levels of brain-derived neurotrophic factor (BDNF): a systematic review of experimental studies in the elderly. *Arch Gerontol Geriatr*. 2013;56:10–5.
28. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*. 2006;443:787–95.
29. Nhu NT, Cheng YJ, Lee SD. Effects of treadmill exercise on neural mitochondrial functions in Parkinson's disease: a systematic review of animal studies. *Biomedicines*. 2021;9:1011.
30. Liang J, Wang C, Zhang H, Huang J, Xie J, Chen N. Exercise-induced benefits for Alzheimer's disease by stimulating mitophagy and improving mitochondrial function. *Front Aging Neurosci*. 2021;13:755665.
31. Severinsen M, Pedersen BK. Muscle-organ crosstalk: the emerging roles of myokines. *Endocr Rev*. 2020;41:594–609.
32. Lee B, Shin M, Park Y, Won SY, Cho KS. Physical exercise-induced myokines in neurodegenerative diseases. *Int J Mol Sci*. 2021;22:5759.
33. Zhao N, Xu B. The beneficial effect of exercise against Alzheimer's disease may result from improved brain glucose metabolism. *Neurosci Lett*. 2021;763:136182.
34. Dalton A, Mermier C, Zuhl M. Exercise influence on the microbiome-gut-brain axis. *Gut Microbes*. 2019;10:555–68.
35. Kolb B, Whishaw IQ. Brain plasticity and behavior. *Annu Rev Psychol*. 1998;49:43–64.
36. Lockhart SN, DeCarli C. Structural imaging measures of brain aging. *Neuropsychol Rev*. 2014;24:271–89.
37. Xiao N, Le QT. Neurotrophic factors and their potential applications in tissue regeneration. *Arch Immunol Ther Exp (Warsz)*. 2016;64:89–99.
38. Jiang L, Zhang H, Wang C, Ming F, Shi X, Yang M. Serum level of brain-derived neurotrophic factor in Parkinson's disease: a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;88:168–74.
39. Karimi N, Ashourizadeh H, Akbarzadeh PB, Haghshomar M, Jouzdani T, Shobeiri P, et al. Blood levels of brain-derived neurotrophic factor (BDNF) in people with multiple sclerosis (MS): a systematic review and meta-analysis. *Mult Scler Relat Disord*. 2022;65:103984.
40. Skaper SD, Facci L, Zusso M, Giusti P. Synaptic plasticity, dementia and Alzheimer disease. *CNS Neurol Disord Drug Targets*. 2017;16:220–33.
41. Terreros-Roncal J, Moreno-Jimenez EP, Flor-Garcia M, Rodriguez-Moreno CB, Trinchero MF, Cafini F, et al. Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. *Science*. 2021;374:1106–13.
42. Moreno-Jimenez EP, Terreros-Roncal J, Flor-Garcia M, Rabano A, Llorens-Martin M. Evidences for adult hippocampal neurogenesis in humans. *J Neurosci*. 2021;41:2541–53.
43. Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V, et al. Human hippocampal neurogenesis persists throughout aging. *Cell Stem Cell*. 2018;22:589–99.
44. Zoubeidi A, Gleave M. Small heat shock proteins in cancer therapy and prognosis. *Int J Biochem Cell Biol*. 2012;44:1646–56.
45. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108:3017–22.
46. Ten BL, Bolandzadeh N, Nagamatsu LS, Hsu CL, Davis JC, Miran-Khan K, et al. Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial. *Br J Sports Med*. 2015;49:248–54.
47. Ma CL, Ma XT, Wang JJ, Liu H, Chen YF, Yang Y. Physical exercise induces hippocampal neurogenesis and prevents cognitive decline. *Behav Brain Res*. 2017;317:332–9.
48. Bettio L, Thacker JS, Hutton C, Christie BR. Modulation of synaptic plasticity by exercise. *Int Rev Neurobiol*. 2019;147:295–322.
49. Barnes J, Bartlett JW, van de Pol LA, Loy CT, Schill RI, Frost C, et al. A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. *Neurobiol Aging*. 2009;30:1711–23.
50. Schaeffer E, Roeben B, Granert O, Hanert A, Liepelt-Scarfone I, Leks E, et al. Effects of exergaming on hippocampal volume and brain-derived neurotrophic factor levels in Parkinson's disease. *Eur J Neurol*. 2022;29:441–9.
51. Frodl T, Strehl K, Carballedo A, Tozzi L, Doyle M, Amico F, et al. Aerobic exercise increases hippocampal subfield volumes in younger adults and prevents volume decline in the elderly. *Brain Imaging Behav*. 2020;14:1577–87.
52. Kim YS, Shin SK, Hong SB, Kim HJ. The effects of strength exercise on hippocampus volume and functional fitness of older women. *Exp Gerontol*. 2017;97:22–8.
53. Cariati I, Bonanni R, Pallone G, Scimeca M, Frank C, Tancredi V, et al. Hippocampal adaptations to continuous aerobic training: a functional and ultrastructural evaluation in a young murine model. *J Funct Morphol Kinesiol*. 2021;6:101.
54. Johansson ME, Cameron I, Van der Kolk NM, de Vries NM, Klimars E, Toni I, et al. Aerobic exercise alters brain function and structure in Parkinson's disease: a randomized controlled trial. *Ann Neurol*. 2022;91:203–16.
55. Prakash RS, Snook EM, Motl RW, Kramer AF. Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis. *Brain Res*. 2010;1341:41–51.
56. Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, et al. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. *Neurology*. 2010;75:1415–22.
57. Alfini AJ, Weiss LR, Nielson KA, Verber MD, Smith JC. Resting cerebral blood flow after exercise training in mild cognitive impairment. *J Alzheimers Dis*. 2019;67:671–84.

58. Tsai CL, Ukropec J, Ukrovcova B, Pai MC. An acute bout of aerobic or strength exercise specifically modifies circulating exerkine levels and neurocognitive functions in elderly individuals with mild cognitive impairment. *Neuroimage Clin.* 2018;17:272–84.
59. Adam D, Ramlı A, Shahar S. Effectiveness of a combined dance and relaxation intervention on reducing anxiety and depression and improving quality of life among the cognitively impaired elderly. *Sultan Qaboos Univ Med J.* 2016;16:e47–53.
60. Nagamatsu LS, Handy TC, Hsu CL, Voss M, Liu-Ambrose T. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. *Arch Intern Med.* 2012;172:666–8.
61. Kujawski S, Kujawska A, Kozakiewicz M, Jakovljevic DG, Stankiewicz B, Newton JL, et al. Effects of sitting callisthenic balance and resistance exercise programs on cognitive function in older participants. *Int J Environ Res Public Health.* 2022;19:14925.
62. Ruiz-Gonzalez D, Hernandez-Martinez A, Valenzuela PL, Morales JS, Soriano-Maldonado A. Effects of physical exercise on plasma brain-derived neurotrophic factor in neurodegenerative disorders: a systematic review and meta-analysis of randomized controlled trials. *Neurosci Biobehav Rev.* 2021;128:394–405.
63. Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. *Int J Mol Sci.* 2020;21:7777.
64. Jones EJ, Chiou SY, Atherton PJ, Phillips BE, Piasecki M. Ageing and exercise-induced motor unit remodelling. *J Physiol.* 2022;600:1839–49.
65. Rahmani F, Saghazadeh A, Rahmani M, Teixeira AL, Rezaei N, Aghamolaii V, et al. Plasma levels of brain-derived neurotrophic factor in patients with Parkinson disease: a systematic review and meta-analysis. *Brain Res.* 2019;1704:127–36.
66. Xie B, Zhou H, Liu W, Yu W, Liu Z, Jiang L, et al. Evaluation of the diagnostic value of peripheral BDNF levels for Alzheimer's disease and mild cognitive impairment: results of a meta-analysis. *Int J Neurosci.* 2020;130:218–30.
67. Thoenen H. Neurotrophins and neuronal plasticity. *Science.* 1995;270:593–8.
68. Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. *Handb Exp Pharmacol.* 2014;220:223–50.
69. Arazi H, Babaei P, Moghimi M, Asadi A. Acute effects of strength and endurance exercise on serum BDNF and IGF-1 levels in older men. *Bmc Geriatr.* 2021;21:50.
70. Behrendt T, Kirschnick F, Kroger L, Beileke P, Rezepin M, Brigadski T, et al. Comparison of the effects of open vs. closed skill exercise on the acute and chronic BDNF, IGF-1 and IL-6 response in older healthy adults. *Bmc Neurosci.* 2021;22:71.
71. Wrann CD, White JP, Salogiannis J, Laznik-Bogoslavski D, Wu J, Ma D, et al. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. *Cell Metab.* 2013;18:649–59.
72. Belviranli M, Okudan N. Exercise training protects against aging-induced cognitive dysfunction via activation of the hippocampal PGC-1alpha/FNDC5/BDNF pathway. *Neuromolecular Med.* 2018;20:386–400.
73. Lima GB, Doorduın J, Klein HC, Dierckx R, Bromberg E, de Vries E. Brain-derived neurotrophic factor in brain disorders: focus on neuroinflammation. *Mol Neurobiol.* 2019;56:3295–312.
74. Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, Clemenson GD, et al. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science.* 2018;361:eaan8821.
75. Rai SN, Dilnashin H, Birla H, Singh SS, Zahra W, Rathore AS, et al. The role of PI3K/Akt and ERK in neurodegenerative disorders. *Neurotox Res.* 2019;35:775–95.
76. Ahmed S, Kwatra M, Gawali B, Panda SR, Naidu V. Potential role of TrkB agonist in neuronal survival by promoting CREB/BDNF and PI3K/Akt signaling in vitro and in vivo model of 3-nitropropionic acid (3-NP)-induced neuronal death. *Apoptosis.* 2021;26:52–70.
77. Leal G, Comprido D, Duarte CB. BDNF-induced local protein synthesis and synaptic plasticity. *Neuropharmacology.* 2014;76(Pt C):639–56.
78. Huang EJ, Reichardt LF. Trk receptors: roles in neuronal signal transduction. *Annu Rev Biochem.* 2003;72:609–42.
79. Dong C, Waters SB, Holt KH, Pessin JE. SOS phosphorylation and disassociation of the Grb2-SOS complex by the ERK and JNK signaling pathways. *J Biol Chem.* 1996;271:6328–32.
80. Xu L, Zhu L, Zhu L, Chen D, Cai K, Liu Z, et al. Moderate exercise combined with enriched environment enhances learning and memory through BDNF/TrkB signaling pathway in rats. *Int J Environ Res Public Health.* 2021;18:8283.
81. Tomiga Y, Sakai K, Ra SG, Kusano M, Ito A, Uehara Y, et al. Short-term running exercise alters DNA methylation patterns in neuronal nitric oxide synthase and brain-derived neurotrophic factor genes in the mouse hippocampus and reduces anxiety-like behaviors. *Faseb J.* 2021;35:e21767.
82. Venezia AC, Hyer MM, Gasper ER, Roth SM, Quinlan EM. Acute forced exercise increases Bdnf IV mRNA and reduces exploratory behavior in C57BL/6J mice. *Genes Brain Behav.* 2020;19:e12617.
83. Baranowski BJ, Hayward GC, Marko DM, MacPherson R. Examination of BDNF treatment on BACE1 activity and acute exercise on brain BDNF signaling. *Front Cell Neurosci.* 2021;15:665867.
84. Martini F, Regis LM, Goncalves RS, Pregardier KI, Wayne NC. Strength exercise suppresses STZ-induced spatial memory impairment and modulates BDNF/ERK-CAMKII/CREB signalling pathway in the hippocampus of mice. *Cell Biochem Funct.* 2020;38:213–21.
85. Sleiman SF, Henry J, Al-Haddad R, El HL, Abou HE, Stringer T, et al. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body beta-hydroxybutyrate. *Elife.* 2016;5:e15092.
86. Li X, Inoue T, Hayashi M, Maejima H. Exercise enhances the expression of brain-derived neurotrophic factor in the hippocampus accompanied by epigenetic alterations in senescence-accelerated mice prone 8. *Neurosci Lett.* 2019;706:176–81.
87. Shen T, You Y, Joseph C, Mirzaei M, Klistorner A, Graham SL, et al. BDNF polymorphism: a review of its diagnostic and clinical relevance in neurodegenerative disorders. *Aging Dis.* 2018;9:523–36.
88. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF Val66Met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell.* 2003;112:257–69.
89. Brown BM, Castalaneli N, Rainey-Smith SR, Doecke J, Weinborn M, Sohrabi HR, et al. Influence of BDNF Val66Met on the relationship between cardiorespiratory fitness and memory in cognitively normal older adults. *Behav Brain Res.* 2019;362:103–8.
90. Nascimento CM, Pereira JR, Pires DAL, Garuffi M, Ayan C, Kerr DS, et al. Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different BDNF Val66Met genotypes. *J Alzheimers Dis.* 2015;43:81–91.
91. Ieraci A, Madaia AI, Mallei A, Lee FS, Popoli M. Brain-derived neurotrophic factor Val66Met human polymorphism impairs the beneficial exercise-induced neurobiological changes in mice. *Neuropsychopharmacology.* 2016;41:3070–9.
92. Ieraci A, Beggato S, Ferraro L, Barbieri SS, Popoli M. Kynurenine pathway is altered in BDNF Val66Met knock-in mice: effect of physical exercise. *Brain Behav Immun.* 2020;89:440–50.
93. Canivet A, Albinet CT, Andre N, Pylouster J, Rodriguez-Ballesteros M, Kitzis A, et al. Effects of BDNF polymorphism and physical activity on episodic memory in the elderly: a cross sectional study. *Eur Rev Aging Phys Act.* 2015;12:15.
94. Zhu F, Cizeron M, Qiu Z, Benavides-Piccione R, Kopanitsa MV, Skene NG, et al. Architecture of the mouse brain synaptome. *Neuron.* 2018;99:781–99.
95. Thiel G. Synapsin I, synapsin II, and synaptophysin: marker proteins of synaptic vesicles. *Brain Pathol.* 1993;3:87–95.
96. Coley AA, Gao WJ. PSD95: a synaptic protein implicated in schizophrenia or autism? *Prog Neuropsychopharmacol Biol Psychiatry.* 2018;82:187–94.
97. Ahmad M, Polepalli JS, Goswami D, Yang X, Kaeser-Woo YJ, Sudhof TC, et al. Postsynaptic complexin controls AMPA receptor exocytosis during LTP. *Neuron.* 2012;73:260–7.
98. Vasuta C, Caunt C, James R, Samadi S, Schibuk E, Kannangara T, et al. Effects of exercise on NMDA receptor subunit contributions to bidirectional synaptic plasticity in the mouse dentate gyrus. *Hippocampus.* 2007;17:1201–8.
99. Staples MC, Somkuwar SS, Mandyam CD. Developmental effects of wheel running on hippocampal glutamate receptor expression in young and mature adult rats. *Neuroscience.* 2015;305:248–56.

100. Dore K, Carrico Z, Alfonso S, Marino M, Koymans K, Kessels HW, et al. PSD-95 protects synapses from beta-amyloid. *Cell Rep.* 2021;35:109194.
101. Mu L, Cai J, Gu B, Yu L, Li C, Liu QS, et al. Treadmill exercise prevents decline in spatial learning and memory in 3xTg-AD mice through enhancement of structural synaptic plasticity of the hippocampus and prefrontal cortex. *Cells-Basel.* 2022;11:244.
102. Li B, Mao Q, Zhao N, Xia J, Zhao Y, Xu B. Treadmill exercise overcomes memory deficits related to synaptic plasticity through modulating ionic glutamate receptors. *Behav Brain Res.* 2021;414:113502.
103. Liu ZT, Ma YT, Pan ST, Xie K, Shen W, Lin SY, et al. Effects of involuntary treadmill running in combination with swimming on adult neurogenesis in an Alzheimer's mouse model. *Neurochem Int.* 2022;155:105309.
104. Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. *Nat Rev Neurosci.* 2018;19:235–49.
105. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol Rev.* 2014;94:909–50.
106. Mattson MP, Gleichmann M, Cheng A. Mitochondria in neuroplasticity and neurological disorders. *Neuron.* 2008;60:748–66.
107. Menzies FM, Fleming A, Rubinsztein DC. Compromised autophagy and neurodegenerative diseases. *Nat Rev Neurosci.* 2015;16:345–57.
108. Hood DA, Memme JM, Oliveira AN, Triolo M. Maintenance of skeletal muscle mitochondria in health, exercise, and aging. *Annu Rev Physiol.* 2019;81:19–41.
109. Bishop DJ, Botella J, Genders AJ, Lee MJ, Saner NJ, Kuang J, et al. High-intensity exercise and mitochondrial biogenesis: current controversies and future research directions. *Physiology (Bethesda).* 2019;34:56–70.
110. Li PA, Hou X, Hao S. Mitochondrial biogenesis in neurodegeneration. *J Neurosci Res.* 2017;95:2025–9.
111. Gupta VK, You Y, Gupta VB, Klistorner A, Graham SL. TrkB receptor signaling: implications in neurodegenerative, psychiatric and proliferative disorders. *Int J Mol Sci.* 2013;14:10122–42.
112. Horowitz AM, Fan X, Bieri G, Smith LK, Sanchez-Diaz CI, Schroer AB, et al. Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. *Science.* 2020;369:167–73.
113. Marques-Aleixo I, Santos-Alves E, Balca MM, Rizo-Roca D, Moreira PI, Oliveira PJ, et al. Physical exercise improves brain cortex and cerebellum mitochondrial bioenergetics and alters apoptotic, dynamic and auto(mito)phagy markers. *Neuroscience.* 2015;301:480–95.
114. Cai Q, Jeong YY. Mitophagy in Alzheimer's disease and other age-related neurodegenerative diseases. *Cells.* 2020;9:150.
115. Sukhorukov V, Voronkov D, Baranich T, Mudzhiri N, Magnaeva A, Illarionovskin S. Impaired mitophagy in neurons and glial cells during aging and age-related disorders. *Int J Mol Sci.* 2021;22:10251.
116. Chen Y, Dorn GN. PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. *Science.* 2013;340:471–5.
117. Sandoval H, Thiagarajan P, Dasgupta SK, Schumacher A, Prchal JT, Chen M, et al. Essential role for Nix in autophagic maturation of erythroid cells. *Nature.* 2008;454:232–5.
118. Chu CT, Ji J, Dagda RK, Jiang JF, Tyurina YY, Kapralov AA, et al. Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells. *Nat Cell Biol.* 2013;15:1197–205.
119. Matsuda N, Sato S, Shiba K, Okatsu K, Saisho K, Gautier CA, et al. PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. *J Cell Biol.* 2010;189:211–21.
120. Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature.* 2015;524:309–14.
121. Revilla S, Sunol C, Garcia-Mesa Y, Gimenez-Llort L, Sanfeliu C, Cristofol R. Physical exercise improves synaptic dysfunction and recovers the loss of survival factors in 3xTg-AD mouse brain. *Neuropharmacology.* 2014;81:55–63.
122. Koo JH, Kang EB, Oh YS, Yang DS, Cho JY. Treadmill exercise decreases amyloid-beta burden possibly via activation of SIRT-1 signaling in a mouse model of Alzheimer's disease. *Exp Neurol.* 2017;288:142–52.
123. Jang SY, Kang HT, Hwang ES. Nicotinamide-induced mitophagy: event mediated by high NAD⁺/NADH ratio and SIRT1 protein activation. *J Biol Chem.* 2012;287:19304–14.
124. Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Canto C, et al. The NAD(+)/Sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. *Cell.* 2013;154:430–41.
125. Hariharan N, Maejima Y, Nakae J, Paik J, Depinho RA, Sadoshima J. Deacetylation of FoxO by Sirt1 plays an essential role in mediating starvation-induced autophagy in cardiac myocytes. *Circ Res.* 2010;107:1470–82.
126. Das S, Mitrovsky G, Vasanthi HR, Das DK. Antiaging properties of a grape-derived antioxidant are regulated by mitochondrial balance of fusion and fission leading to mitophagy triggered by a signaling network of Sirt1-Sirt3-Foxo3-PINK1-PARKIN. *Oxid Med Cell Longev.* 2014;2014:345105.
127. Hou Y, Wei Y, Lautrup S, Yang B, Wang Y, Cordonnier S, et al. NAD(+) supplementation reduces neuroinflammation and cell senescence in a transgenic mouse model of Alzheimer's disease via cGAS-STING. *Proc Natl Acad Sci U S A.* 2021;118:e2011226118.
128. Nay K, Smiles WJ, Kaiser J, McAloon LM, Loh K, Galic S, et al. Molecular mechanisms underlying the beneficial effects of exercise on brain function and neurological disorders. *Int J Mol Sci.* 2021;22:4052.
129. Sui SX, Williams LJ, Holloway-Kew KL, Hyde NK, Pasco JA. Skeletal muscle health and cognitive function: a narrative review. *Int J Mol Sci.* 2020;22:255.
130. Scisciola L, Fontanella RA, Surina, Cataldo V, Paolisso G, Barbieri M. Sarcopenia and cognitive function: role of myokines in muscle brain cross-talk. *Life (Basel).* 2021;11:173.
131. Islam MR, Young MF, Wrann CD. The role of FNDC5/irisin in the nervous system and as a mediator for beneficial effects of exercise on the brain. In: Spiegelman B, editor. *Hormones, metabolism and the benefits of exercise* [Internet]. Cham: Springer; 2017. p. 93–102.
132. Jodeiri FM, Alvina K. Multiple roles in neuroprotection for the exercise derived myokine irisin. *Front Aging Neurosci.* 2021;13:649929.
133. Wrann CD. FNDC5/irisin - their role in the nervous system and as a mediator for beneficial effects of exercise on the brain. *Brain Plast.* 2015;1:55–61.
134. Moon HJ, Herring SK, Zhao L. Clusterin: a multifaceted protein in the brain. *Neural Regen Res.* 2021;16:1438–9.
135. Rai M, Coleman Z, Curley M, Nityanandam A, Platt A, Robles-Murguía M, et al. Proteasome stress in skeletal muscle mounts a long-range protective response that delays retinal and brain aging. *Cell Metab.* 2021;33:1137–54.
136. Xu B. BDNF (I)rising from exercise. *Cell Metab.* 2013;18:612–4.
137. Islam MR, Valaris S, Young MF, Haley EB, Luo R, Bond SF, et al. Exercise hormone irisin is a critical regulator of cognitive function. *Nat Metab.* 2021;3:1058–70.
138. Waseem R, Shamsi A, Mohammad T, Hassan MI, Kazim SN, Chaudhary AA, et al. FNDC5/irisin: physiology and pathophysiology. *Molecules.* 2022;27:1118.
139. Jandova T, Buendia-Romero A, Polanska H, Hola V, Rihova M, Vetrovsky T, et al. Long-term effect of exercise on irisin blood levels-systematic review and meta-analysis. *Healthcare (Basel).* 2021;9:1438.
140. Qiu S, Cai X, Sun Z, Schumann U, Zugel M, Steinacker JM. Chronic exercise training and circulating irisin in adults: a meta-analysis. *Sports Med.* 2015;45:1577–88.
141. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, et al. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat Med.* 2019;25:165–75.
142. Li DJ, Li YH, Yuan HB, Qu LF, Wang P. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism.* 2017;68:31–42.
143. Bluthgen N, van Bentum M, Merz B, Kuhl D, Hermeijer G. Profiling the MAPK/ERK dependent and independent activity regulated transcriptional programs in the murine hippocampus in vivo. *Sci Rep.* 2017;7:45101.
144. Wiegert JS, Bading H. Activity-dependent calcium signaling and ERK-MAP kinases in neurons: a link to structural plasticity of the nucleus and gene transcription regulation. *Cell Calcium.* 2011;49:296–305.
145. Yang SH, Sharrocks AD, Whitmarsh AJ. MAP kinase signalling cascades and transcriptional regulation. *Gene.* 2013;513:1–13.
146. Sun LN, Qi JS, Gao R. Physical exercise reserved amyloid-beta induced brain dysfunctions by regulating hippocampal neurogenesis and inflammatory response via MAPK signaling. *Brain Res.* 2018;1697:1–9.

147. Liu H, Jin X, Yin X, Jin N, Liu F, Qian W. PKA-CREB signaling suppresses tau transcription. *J Alzheimers Dis.* 2015;46:239–48.
148. Kandel ER. The molecular biology of memory: cAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. *Mol Brain.* 2012;5:14.
149. Lee SS, Kim CJ, Shin MS, Lim BV. Treadmill exercise ameliorates memory impairment through ERK-Akt-CREB-BDNF signaling pathway in cerebral ischemia gerbils. *J Exerc Rehabil.* 2020;16:49–57.
150. Ko IG, Kim SE, Hwang L, Jin JJ, Kim CJ, Kim BK, et al. Late starting treadmill exercise improves spatial leaning ability through suppressing CREP/BDNF/TrkB signaling pathway following traumatic brain injury in rats. *J Exerc Rehabil.* 2018;14:327–34.
151. Moon HY, Becke A, Berron D, Becker B, Sah N, Benoni G, et al. Running-induced systemic cathepsin b secretion is associated with memory function. *Cell Metab.* 2016;24:332–40.
152. Hu S, Shen P, Chen B, Tian SW, You Y. Apelin-13 reduces lipopolysaccharide-induced neuroinflammation and cognitive impairment via promoting glucocorticoid receptor expression and nuclear translocation. *Neurosci Lett.* 2022;788:136850.
153. Cervenka I, Agudelo LZ, Ruas JL. Kynurenes: tryptophan's metabolites in exercise, inflammation, and mental health. *Science.* 2017;357:eaaf9794.
154. Wu ZC, Yu JT, Li Y, Tan L. Clusterin in Alzheimer's disease. *Adv Clin Chem.* 2012;56:155–73.
155. De Miguel Z, Khoury N, Betley MJ, Lehallier B, Willoughby D, Olsson N, et al. Exercise plasma boosts memory and dampens brain inflammation via clustering. *Nature.* 2021;600:494–9.
156. Pohlkamp T, Wasser CR, Herz J. Functional roles of the interaction of APP and lipoprotein receptors. *Front Mol Neurosci.* 2017;10:54.
157. Foster EM, Dangla-Valls A, Lovestone S, Ribe EM, Buckley NJ. Clusterin in Alzheimer's disease: mechanisms, genetics, and lessons from other pathologies. *Front Neurosci.* 2019;13:164.
158. Yu JT, Tan L. The role of clusterin in Alzheimer's disease: pathways, pathogenesis, and therapy. *Mol Neurobiol.* 2012;45:314–26.
159. Wojtas AM, Carlomagno Y, Sens JP, Kang SS, Jensen TD, Kurti A, et al. Clusterin ameliorates tau pathology in vivo by inhibiting fibril formation. *Acta Neuropathol Commun.* 2020;8:210.
160. de Retana SF, Marazuela P, Sole M, Colell G, Bonaterra A, Sanchez-Quesada JL, et al. Peripheral administration of human recombinant ApoJ/clusterin modulates brain beta-amyloid levels in APP23 mice. *Alzheimers Res Ther.* 2019;11:42.
161. Lenzi C, Ramazzina I, Russo I, Filippini A, Bettuzzi S, Rizzi F. The down-regulation of clusterin expression enhances the alphaSynuclein aggregation process. *Int J Mol Sci.* 2020;21:7181.
162. Davitz MA, Hereld D, Shak S, Krakow J, Englund PT, Nussenzweig V. A glycan-phosphatidylinositol-specific phospholipase D in human serum. *Science.* 1987;238:81–4.
163. Masuda S, Fujishima Y, Maeda N, Tsugawa-Shimizu Y, Nakamura Y, Tanaka Y, et al. Impact of glycosylphosphatidylinositol-specific phospholipase D on hepatic diacylglycerol accumulation, steatosis, and insulin resistance in diet-induced obesity. *Am J Physiol Endocrinol Metab.* 2019;316:E239–50.
164. Zhang K, Zhu H, Wang L, Yang H, Pan H, Gong F. Serum glypican4 and glycosylphosphatidylinositol-specific phospholipase D levels are associated with adipose tissue insulin resistance in obese subjects with different glucose metabolism status. *J Endocrinol Investig.* 2021;44:781–90.
165. Naghibalhossaini F, Ebadi P. Evidence for CEA release from human colon cancer cells by an endogenous GPI-PLD enzyme. *Cancer Lett.* 2006;234:158–67.
166. Ferreira LF, Laitano O. Regulation of NADPH oxidases in skeletal muscle. *Free Radic Biol Med.* 2016;98:18–28.
167. Yan L, Wei JA, Yang F, Wang M, Wang S, Cheng T, et al. Physical exercise prevented stress-induced anxiety via improving brain RNA methylation. *Adv Sci (Weinh).* 2022;9:e2105731.
168. Lu Y, Ren J, Cui S, Chen J, Huang Y, Tang C, et al. Cerebral glucose metabolism assessment in rat models of Alzheimer's disease: an 18F-FDG-PET study. *Am J Alzheimers Dis Other Dement.* 2016;31:333–40.
169. Chen Z, Zhong C. Decoding Alzheimer's disease from perturbed cerebral glucose metabolism: implications for diagnostic and therapeutic strategies. *Prog Neurobiol.* 2013;108:21–43.
170. Camandola S, Mattson MP. Brain metabolism in health, aging, and neurodegeneration. *Embo J.* 2017;36:1474–92.
171. Pang R, Wang X, Pei F, Zhang W, Shen J, Gao X, et al. Regular exercise enhances cognitive function and intracephalic GLUT expression in Alzheimer's disease model mice. *J Alzheimers Dis.* 2019;72:83–96.
172. Jiang H, Jia D, Zhang B, Yang W, Dong Z, Sun X, et al. Exercise improves cardiac function and glucose metabolism in mice with experimental myocardial infarction through inhibiting HDAC4 and upregulating GLUT1 expression. *Basic Res Cardiol.* 2020;115:28.
173. Bosco D, Fava A, Plastino M, Montalcini T, Pujia A. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. *J Cell Mol Med.* 2011;15:1807–21.
174. Brown C, Pemberton S, Babin A, Abdulhameed N, Noonan C, Brown MB, et al. Insulin blood-brain barrier transport and interactions are greater following exercise in mice. *J Appl Physiol.* 1985;2022(132):824–34.
175. Zhang Y, Huang NQ, Yan F, Jin H, Zhou SY, Shi JS, et al. Diabetes mellitus and Alzheimer's disease: GSK-3beta as a potential link. *Behav Brain Res.* 2018;339:57–65.
176. Liu W, Xue X, Xia J, Liu J, Qi Z. Swimming exercise reverses CUMS-induced changes in depression-like behaviors and hippocampal plasticity-related proteins. *J Affect Disord.* 2018;227:126–35.
177. Cai Z, Zhao Y, Zhao B. Roles of glycogen synthase kinase 3 in Alzheimer's disease. *Curr Alzheimer Res.* 2012;9:864–79.
178. Takashima A. GSK-3 is essential in the pathogenesis of Alzheimer's disease. *J Alzheimers Dis.* 2006;9:309–17.
179. Rippin I, Bonder K, Joseph S, Sarsor A, Vaks L, Eldar-Finkelman H. Inhibition of GSK-3 ameliorates the pathogenesis of Huntington's disease. *Neurobiol Dis.* 2021;154:105336.
180. Fang W, Gao G, Zhao H, Xia Y, Guo X, Li N, et al. Role of the Akt/GSK-3beta/CRMP-2 pathway in axon degeneration of dopaminergic neurons resulting from MPP+ toxicity. *Brain Res.* 2015;1602:9–19.
181. Narkar VA, Downes M, Yu RT, Emblar E, Wang YX, Banayo E, et al. AMPK and PPARdelta agonists are exercise mimetics. *Cell.* 2008;134:405–15.
182. Kang EB, Cho JY. Effect of treadmill exercise on PI3K/AKT/mTOR, autophagy, and Tau hyperphosphorylation in the cerebral cortex of NSE/Htau23 transgenic mice. *J Exerc Nutr Biochem.* 2015;19:199–209.
183. Zheng Q, Kong LH, Yu CC, He RY, Wang XS, Jiang T, et al. Effects of electroacupuncture on cognitive function and neuronal autophagy in rats with D-galactose induced Alzheimer's disease. *Zhen Ci Yan Jiu.* 2020;45:689–95.
184. Ghosh S, Castillo E, Frias ES, Swanson RA. Bioenergetic regulation of microglia. *Glia.* 2018;66:1200–12.
185. Piers TM, Cosker K, Mallach A, Johnson GT, Guerreiro R, Hardy J, et al. A locked immunometabolic switch underlies TREM2 R47H loss of function in human iPSC-derived microglia. *Faseb J.* 2020;34:2436–50.
186. Colonna M. TREMs in the immune system and beyond. *Nat Rev Immunol.* 2003;3:445–53.
187. Ulrich JD, Holtzman DM. TREM2 function in Alzheimer's disease and neurodegeneration. *ACS Chem Neurosci.* 2016;7:420–7.
188. Qin Q, Teng Z, Liu C, Li Q, Yin Y, Tang Y. TREM2, microglia, and Alzheimer's disease. *Mech Ageing Dev.* 2021;195:111438.
189. Sheng L, Chen M, Cai K, Song Y, Yu D, Zhang H, et al. Microglial Trem2 induces synaptic impairment at early stage and prevents amyloidosis at late stage in APP/PS1 mice. *Faseb J.* 2019;33:10425–42.
190. Yu CJ, Wang M, Li RY, Wei T, Yang HC, Yin YS, et al. TREM2 and microglia contribute to the synaptic plasticity: from physiology to pathology. *Mol Neurobiol.* 2023;60:512–23.
191. Zhang SS, Zhu L, Peng Y, Zhang L, Chao FL, Jiang L, et al. Long-term running exercise improves cognitive function and promotes microglial glucose metabolism and morphological plasticity in the hippocampus of APP/PS1 mice. *J Neuroinflamm.* 2022;19:34.
192. Aho V, Houser MC, Pereira P, Chang J, Rudi K, Paulin L, et al. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. *Mol Neurodegener.* 2021;16:6.
193. Dinan TG, Cryan JF. Brain-gut-microbiota axis and mental health. *Psychosom Med.* 2017;79:920–6.
194. Morais LH, Schreiber HT, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol.* 2021;19:241–55.
195. Blacher E, Bashiardes S, Shapiro H, Rothschild D, Mor U, Dori-Bachash M, et al. Potential roles of gut microbiome and metabolites in modulating ALS in mice. *Nature.* 2019;572:474–80.

196. Cox LM, Maghzi AH, Liu S, Tankou SK, Dhang FH, Willocq V, et al. Gut microbiome in progressive multiple sclerosis. *Ann Neurol*. 2021;89:1195–211.
197. Ou Z, Deng L, Lu Z, Wu F, Liu W, Huang D, et al. Protective effects of *Akkermansia muciniphila* on cognitive deficits and amyloid pathology in a mouse model of Alzheimer's disease. *Nutr Diabetes*. 2020;10:12.
198. Yuan S, Yang J, Jian Y, Lei Y, Yao S, Hu Z, et al. Treadmill exercise modulates intestinal microbes and suppresses LPS displacement to alleviate neuroinflammation in the brains of APP/PS1 mice. *Nutrients*. 2022;14:4134.
199. Zhai Q, Feng S, Arjan N, Chen W. A next generation probiotic, *Akkermansia muciniphila*. *Crit Rev Food Sci Nutr*. 2019;59:3227–36.
200. Wu W, Lv L, Shi D, Ye J, Fang D, Guo F, et al. Protective effect of *Akkermansia muciniphila* against immune-mediated liver injury in a mouse model. *Front Microbiol*. 2017;8:1804.
201. Campbell SC, Wisniewski PJ, Noji M, McGuinness LR, Haggblom MM, Lightfoot SA, et al. The effect of diet and exercise on intestinal integrity and microbial diversity in mice. *PLoS One*. 2016;11:e150502.
202. Kim MS, Kim Y, Choi H, Kim W, Park S, Lee D, et al. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut*. 2020;69:283–94.
203. Jackson A, Forsyth CB, Shaikh M, Voigt RM, Engen PA, Ramirez V, et al. Diet in Parkinson's disease: critical role for the microbiome. *Front Neurol*. 2019;10:1245.
204. Ning Q, Liu Z, Wang X, Zhang R, Zhang J, Yang M, et al. Neurodegenerative changes and neuroapoptosis induced by systemic lipopolysaccharide administration are reversed by dexmedetomidine treatment in mice. *Neurol Res*. 2017;39:357–66.
205. Shin HE, Kwak SE, Zhang DD, Lee J, Yoon KJ, Cho HS, et al. Effects of treadmill exercise on the regulation of tight junction proteins in aged mice. *Exp Gerontol*. 2020;141:111077.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

